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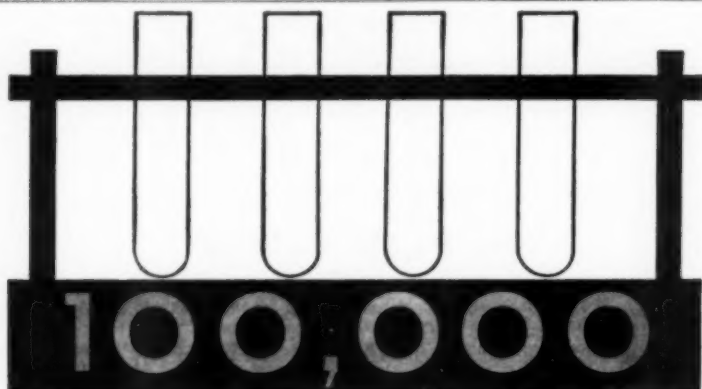
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2. Getting, V. A., and others: *Diabetes* 1:194, 1952.

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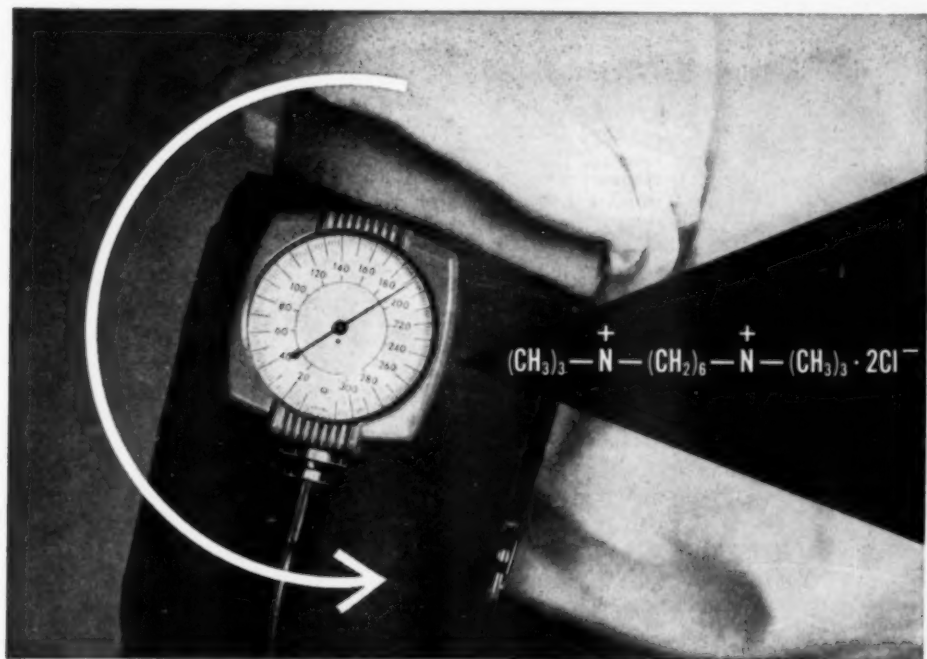
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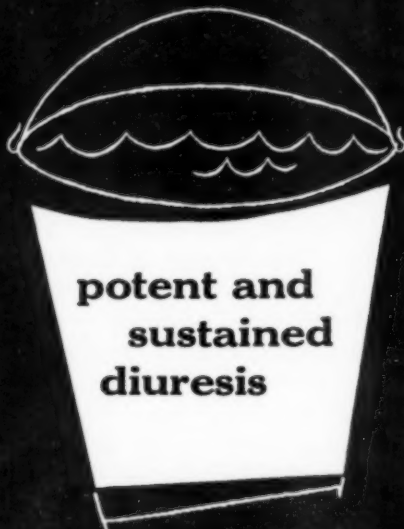
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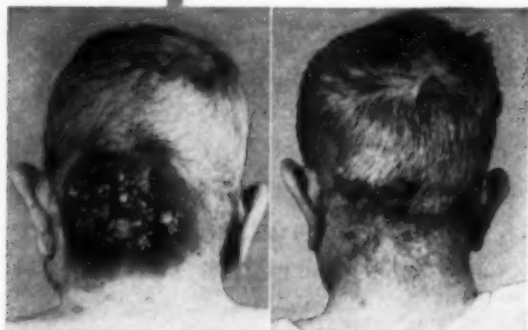
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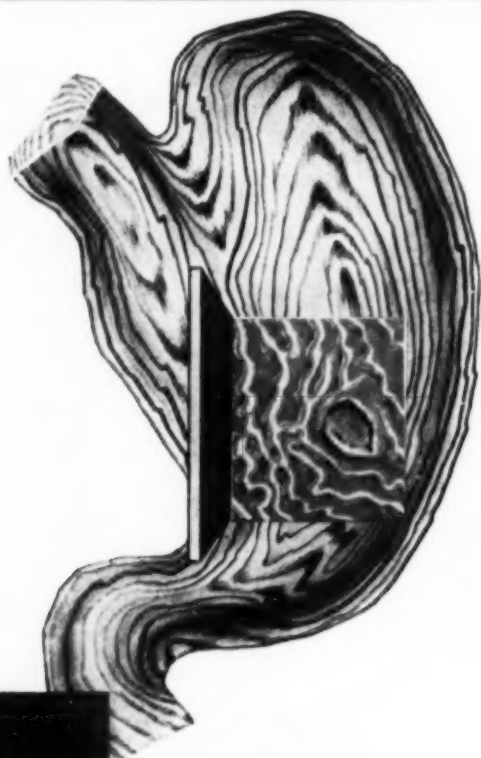


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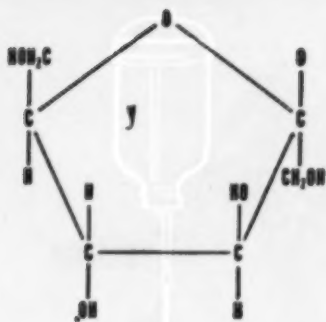
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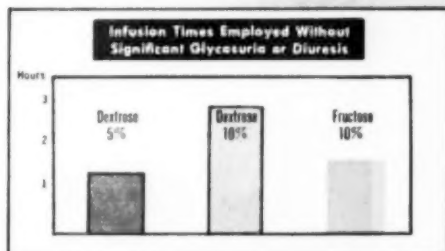


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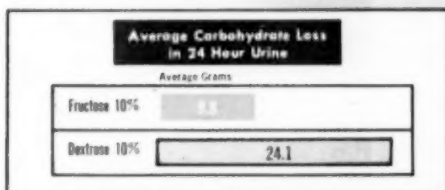
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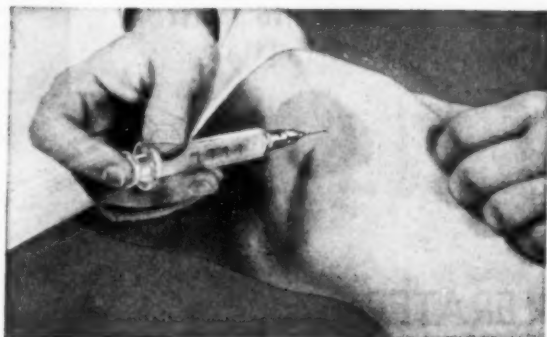
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Literature on Request

1. Brown, E. M., Frain, J. B., Udell, L., and Hollander, J. L.: Paper presented at Annual Meeting, American Rheumatism Association, Chicago, Ill., June 6, 1952.

HYDROCORTONE is the registered trade-mark of Merck & Co., Inc. for its brand of hydrocortisone. This substance was first made available to the world through Merck research and production.



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REPEATEDLY SHOWN and proven by objective tests on human subjects¹ — this is one of the most effective of all the commonly known Xanthine derivatives. Because of the enteric coating it may be used with marked freedom from the gastric distress characteristic of ordinary Xanthine therapy. Thus THESODATE, with its reasonable prescription price also, enjoys a greater patient acceptability.

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* (7½ gr.) 0.5 Gm. * (3¼ gr.) 0.25 Gm.

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* In capsule form also, bottles of 25 and 100.

1. Riseman, J. E. P. and Brown, M. G. Arch. Int. Med. 60: 100, 1937

2. Brown, M. G. and Riseman, J. E. P. JAMA 109: 256, 1937.

3. Riseman, J. E. P. N. E. J. Med. 229: 670, 1943.

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1. Lehr, D.: Brit. M. J.: 2: 543-548, 1948.

2. Lehr, D.: Brit. M. J.: 2: 601, 1950.

3. Hawking, F., and Lawrence, J. S.:
The Sulfonamides, New York, Grune
and Stratton, 1951.

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Assay 234; 235

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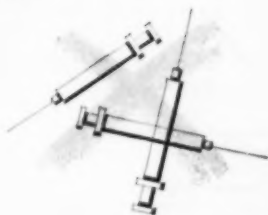
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Thiamine Mononitrate.....	6 mg.
Riboflavin.....	6 mg.
Nicotinamide.....	30 mg.
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Vitamin B ₁₂ (as vitamin B ₁₂ concentrate).....	2 mcg.
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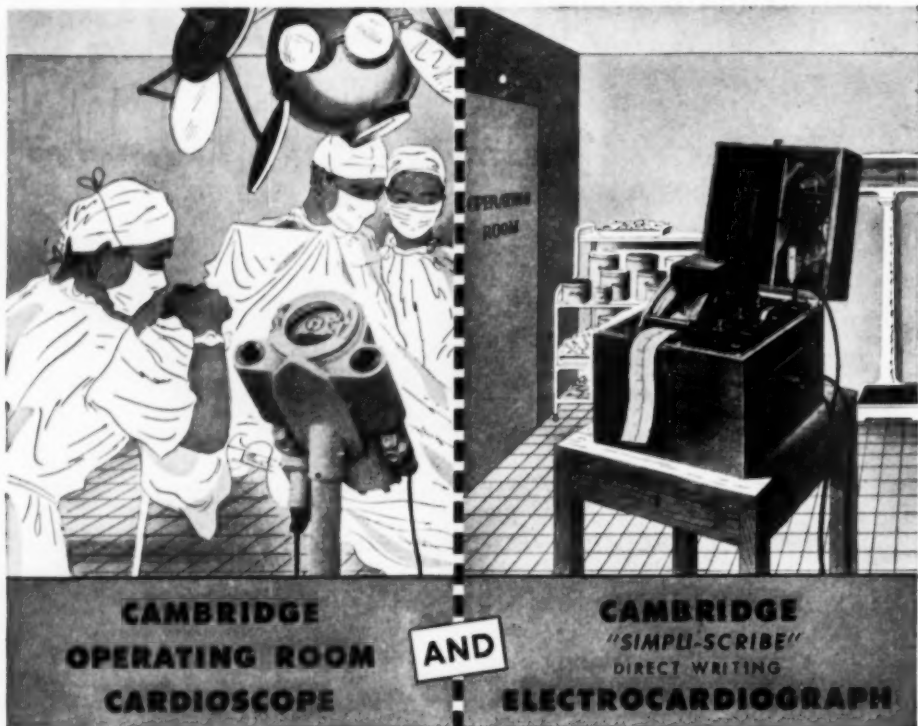
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Ferric ammonium citrate	200.0 mg.
Vitamin B ₁₂ U.S.P. (crystalline)	4.0 mcg.
Extractive as obtained from of fresh gastric tissue	450.0 mg.
Folic acid	0.33 mg.
Thiamine HCl (B ₁)	1.5 mg.
Riboflavin (B ₂)	1.0 mg.
Pyridoxine HCl (B ₆)	0.2 mg.

Suggested dosage:

Adults: 1 to 2 teaspoonfuls

Children: $\frac{1}{2}$ to 1 teaspoonful

Three times daily, or more as required.

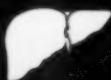


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diabetes	frequent ++++	frequent +++	Methischol as adjunct to diet. Insulin as necessary.
atherosclerosis	frequent +++	frequent ++++	Methischol and high protein, low fat diet.
coronary disease	frequent +++	frequent ++++	Methischol as adjunct to high protein, low fat diet and specific therapy.
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... because it provides vitamin B₁₂ and liver fractions in addition to choline, methionine and inositol.

... helps normalize liver function, increase phospholipid turnover, reduce fatty deposits, and stimulate regeneration of new liver cells ...

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the suggested daily therapeutic dose of 9 capsules or 3 tablespoonfuls of Methischol provides:

Choline Dihydrogen Citrate*	2.5 Gm.
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Liver Concentrate and Desiccated Liver** 0.78 Gm.

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Relieves pain in approximately 3 of every 4 cases within a few days of commencing treatment

Produces functional improvement in many cases by reducing swelling and spasm and increasing mobility

Has favorable effect in virtually all forms of arthritis and many types of painful musculoskeletal disorders

Maintains effectiveness for as long as treatment is continued

Effective by mouth, thus well adapted to routine use in either bedridden or ambulatory patients

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A selection from the bibliography on BUTAZOLIDIN... (1) Freyberg, R.; Kidd, E. C., and Boyce, K. C.: Studies of Butazolidin and Butapyrin in Patients with Rheumatic Diseases. Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, June 6, 1952. (2) Kusell, W. C., and others: Phenylbutazone (Butazolidin) in Rheumatoid Arthritis and Gout, J.A.M.A. 149:729, 1952. (3) Kusell, W. C., and Schaffarick, R. W.: Butapyrin in Gout, Stanford M. Bull. 9:194, 1951. (4) Kusell, W. C., and Schaffarick, R. W.: Phenylbutazone (Butazolidin), Bull. Rheumat. Dis. 3:23, 1952. (5) Kusell, W. C., and Schaffarick, R. W.: Phenylbutazone (Butazolidin) and Butapyrin in Arthritis and Gout, California Med. 77:319, 1952. (6) Smith, C. H., and Kunz, H. G.: Butazolidin in Rheumatoid Disorders, J. M. Soc. New Jersey 49:306, 1952. (7) Steinbrocker, O., and others: Phenylbutazone Therapy of Arthritis and Other Painful Musculoskeletal Disorders, J.A.M.A. 150:1087, 1952. (8) Stephens, C. A. L., Jr., and others: Benefits and Toxicity of Phenylbutazone (Butazolidin)® in Rheumatoid Arthritis, J.A.M.A. 150:1084, 1952.

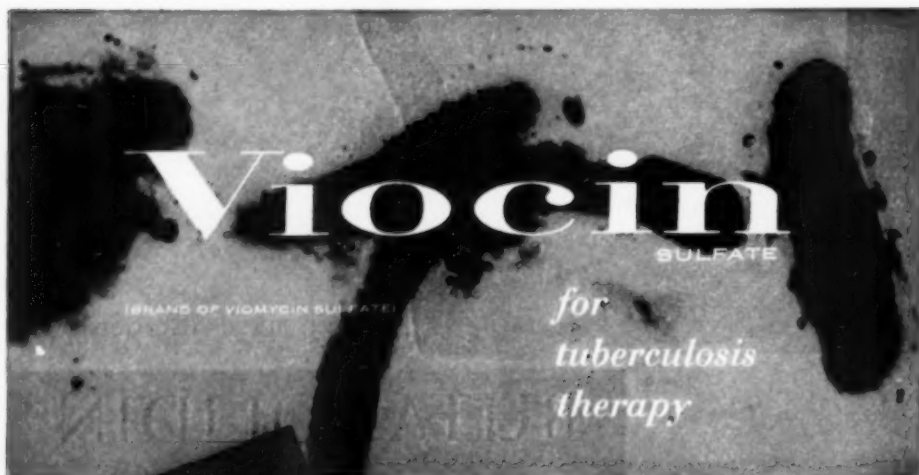


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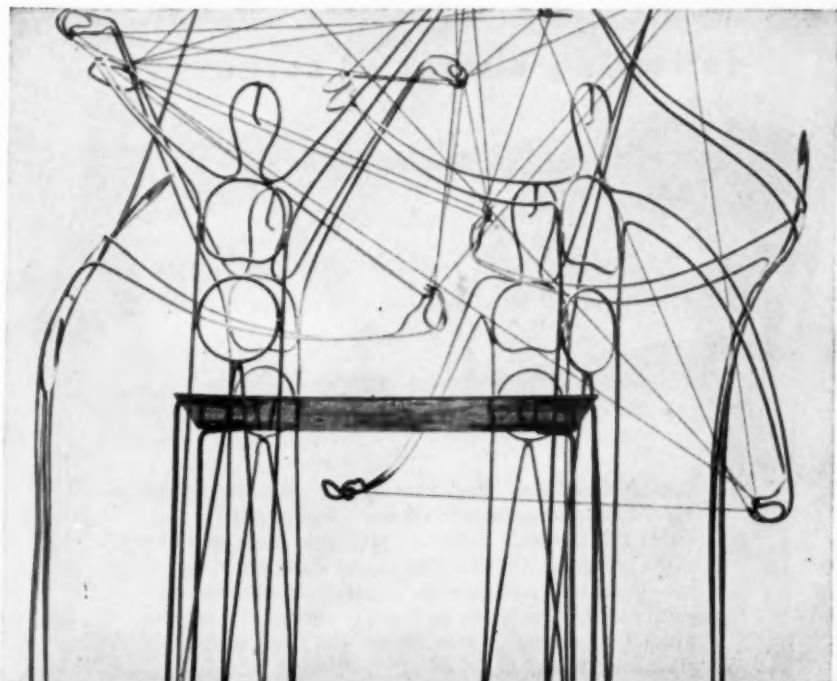
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1. Cantor, A. J., *Am. J. Proctol.* 3:204-210, (Sept.) 1952.

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Aminophylline 5.0 gr.
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* Perloff W. H. Am. J. Obst. & Gynec. 57:684 (Oct.) 1949.

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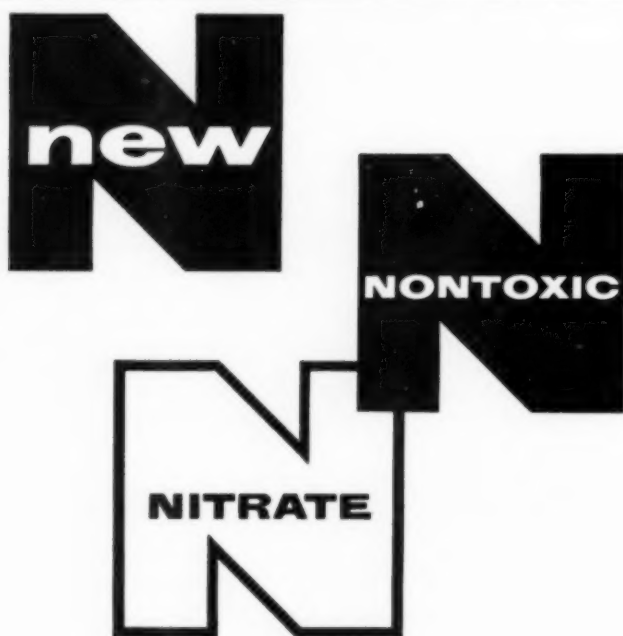
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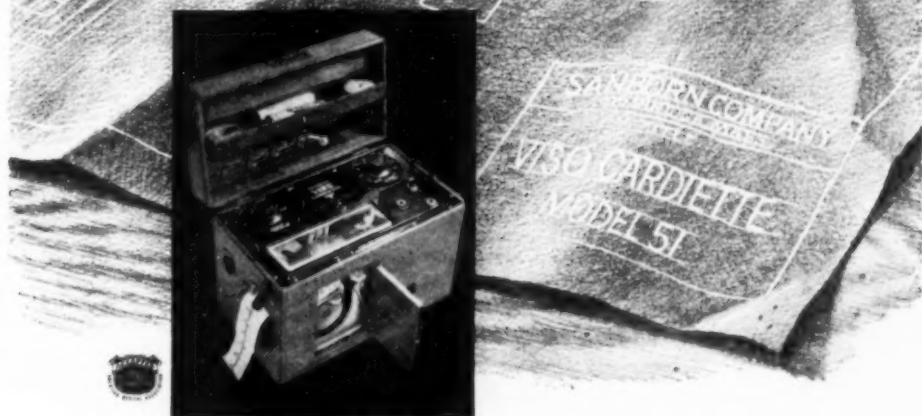
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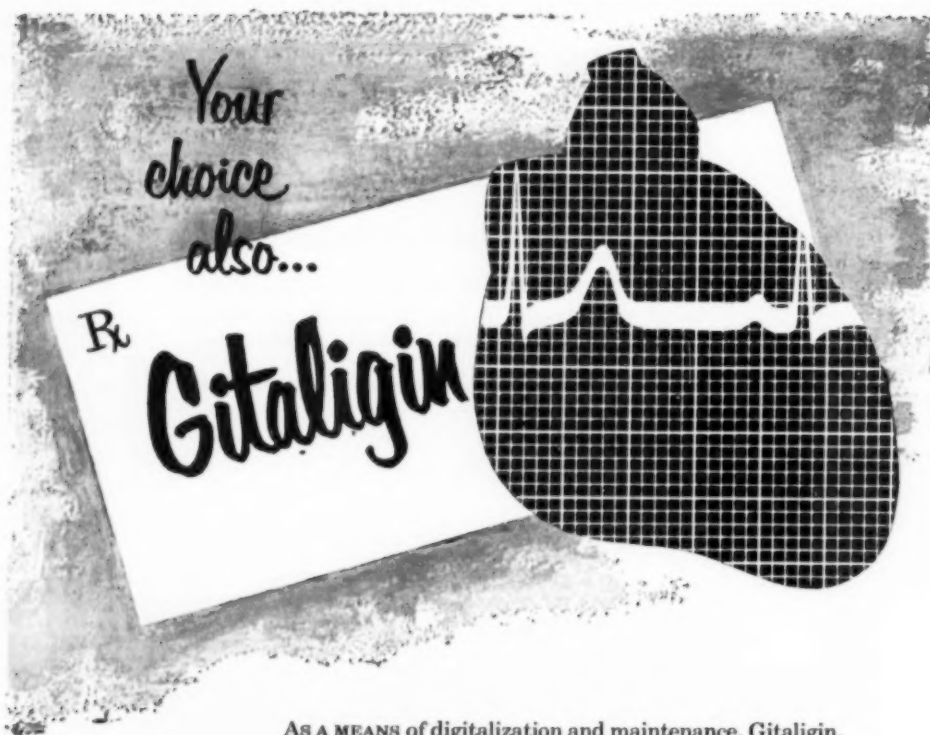
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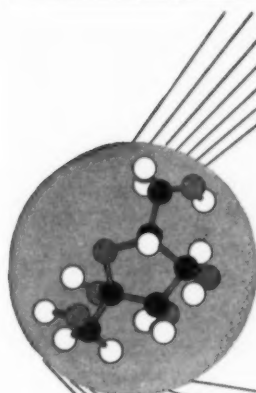


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THE MANAGEMENT OF MALIGNANT HYPERTENSION*

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INTRODUCTION

HYPERTENSION varies strikingly in its clinical course. One of the unexplained vagaries of this condition is the fact that in some instances the disease may be most benign, with little vascular deterioration for a period of 10 to 20 years, while in other cases such deterioration may occur within a few years. One variety of hypertensive disease has been singled out as being particularly ominous and has been designated as malignant, because the downward course is usually measured in months rather than in years. Occurrence of the malignant phase may be detected by the appearance of papilledema, although in some cases the blood urea nitrogen may rise prior to the development of papilledema. Not all patients with hypertension whose course is rapidly downward have papilledema, although in our experience the incidence of such patients has been lower than the 20 per cent noted by Goldring and Chasis.¹ That papilledema alone is a clear indication of a subsequent unfavorable course was first demonstrated by the work of Keith and Wagener.² In a recent study of the prognosis of hypertension with papilledema,³ we found that only three of 91 patients who received symptomatic treatment alone survived 30 months.

On the basis of this knowledge, therefore, how should the physician who is confronted with a patient with hypertension and papilledema proceed in treatment?

The first step is rapid investigation to determine (1) the presence of a correctable etiologic agent or condition, and (2) the functional integrity of

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the vital organs, particularly of the kidney and the heart. Correctable reversible conditions in which malignant hypertension may occur include the following:

1. *Unilateral atrophic kidney, often with pyelonephritis:* As Smith⁴ pointed out, the proved instances of hypertension cured by removal of a diseased kidney are relatively few indeed. Nevertheless, a number of well documented cases of malignant hypertension associated with unilateral atrophic pyelonephritis have been reported.⁵⁻⁸ In our own series the combination was found in two patients, in both of whom the malignant phase was abolished by unilateral nephrectomy. In the first patient the blood pressure returned to normal and the patient was well 10 years later. In the second, although the blood pressure did not return to normal, the papilledema disappeared, vision was restored and the patient was well for a number of months. At that time the malignant phase recurred after a pelvic operation was performed for an incidental severe condition. In all cases of malignant hypertension of undetermined etiology, radiologic studies should be made to exclude the presence of an atrophic kidney which might be treated surgically.

2. *Pheochromocytoma:* In some instances this rare cause of hypertension may be associated with papilledema and a rapid downward course from renal failure. This combination occurred in one of 138 patients with hypertension and papilledema seen in our clinic over a 15 year period. The present diagnostic tests, such as the histamine and benzodioxane tests, were not known at that time and the diagnosis was not made during life. A similar case was reported by Hatch and his associates.⁹

3. *Visceral angitis* occasionally may be associated with hypertension, papilledema and renal failure. Consideration of the possibility of this disease, with attention to its clinical manifestations, including the characteristic urinary sediment described by Krupp,¹⁰ and examination of the blood and bone marrow for lupus erythematosus cells, may aid in the recognition of this disease. Whether the use of cortisone will reverse the vascular manifestations is still a disputed point.

4. *Unilateral hydronephrosis:* Loeb¹¹ described a case of renal insufficiency in which an unsuspected hydronephrosis secondary to aberrant renal arteries was discovered at postmortem examination, and commented on the importance of recognizing reversible renal causes of hypertension. No instances of unilateral hydronephrosis were noted in our series, but one patient with bilateral hydronephrosis secondary to congenital stricture of the bladder neck was treated by transurethral resection and subsequently by hexamethonium, with excellent results (Case No. 115).

5. *Cushing's disease:* This also is a rare cause of hypertension. In our series of 138 cases we encountered only one patient with Cushing's disease and papilledema. Cushing's disease has a characteristic clinical picture, and the diagnosis can be further established by demonstrating evidences of

adrenal cortical hyperactivity. Surgical treatment is often curative and therefore this disease must be kept in mind.

6. *Acute glomerulonephritis*: This condition may be confused with the malignant phase of essential hypertension, and at times the differentiation is impossible. The occurrence at a younger age, the presence of red blood cell casts in the urine, and the history of a recent streptococcal throat infection, followed by edema of the eyes and hands about the time of the onset of hypertension, all indicate a diagnosis of acute glomerulonephritis. The prognosis is, of course, much more favorable in acute glomerulonephritis; and when hypertension with papilledema is seen in a young individual, the possibility of acute nephritis must always be considered.

7. *Coarctation of the aorta and polycystic kidneys*: In reviewing the possible causes of hypertension, it may be noted that none of the patients with either of these two conditions seen at the University of California Hospital in the past 15 years had papilledema.

STATUS OF THE KIDNEY

The importance of the kidney in malignant hypertension has been stressed by a number of observers, notably Peet and Isberg¹² and Page and Taylor.¹³ Peet emphasized that only those patients whose renal function was normal survived five years following sympathectomy, while Page noted that only those patients whose renal function was greater than 50 per cent of normal survived three years following pyrogen therapy of malignant hypertension. Of the 91 patients in our series who received symptomatic treatment alone, no patient who showed significant impairment of renal function when he was first seen survived 30 months. Of the 91 patients, each of the three patients who survived 30 months had normal renal function at the time papilledema was discovered. Furthermore, when renal impairment is severe, certain therapeutic procedures, such as rigid restriction of sodium and sympathectomy, are contraindicated because of the immediate hazards to the patient.

Cardiac, cerebral or vascular complications may be the immediate cause of death, but the majority of patients with malignant hypertension die of uremia. Therefore, determination of the functional integrity of the kidney is most important, not only because deterioration in function is responsible for most of the deaths but also because renal failure may develop very rapidly and prevent the use of therapeutic measures which might otherwise be helpful. Papilledema may be a complication in any of the diseases which cause hypertension; when it occurs in chronic glomerulonephritis or chronic pyelonephritis, the downward course is particularly rapid. Nevertheless, with modern therapeutic measures, the fact that the patient with hypertension and papilledema has underlying chronic renal disease does not make the prognosis hopeless, as will be shown later. Recognition of the malignant phase

should be prompt, however, and treatment should be instituted without delay before irreversible renal failure has occurred.

After it has been established that the patient has satisfactory renal function, and after a careful investigation has failed to reveal any of the specific reversible conditions described previously, what methods of treatment are available to the physician?

PSYCHOTHERAPY

Reiser and his associates¹⁴ noted that the time of onset of the malignant phase frequently appeared to be related to the occurrence of a significant emotional event in the life of the patient, and stated that in six of 12 patients with malignant hypertension psychotherapy resulted in reversal of papilledema. In our unpublished data¹⁵ we have evidence which seems to support Reiser's observation that the malignant phase may be precipitated by unusual emotional events; however, papilledema was not reversed in the four patients in our series who were treated by a psychoanalyst, nor did these patients survive. Since the concept of hypertension as a psychosomatic disease is still based on hypothesis rather than proved fact, it is unwise at the present time to treat a patient with malignant hypertension solely by psychotherapy. If such treatment is ineffective, valuable time will have been lost and serious vascular deterioration may have occurred. Attention to the emotional problems of the patient in conjunction with other therapeutic methods, in our opinion, is highly desirable.

LOW SODIUM DIET

This has been a highly controversial matter, but Kempner¹⁶ has described reversal of papilledema in 17 of 23 patients with malignant hypertension given prolonged treatment with a rice diet; the papilledema disappeared partially in five patients and remained unchanged in one. We have used the rice or low sodium diet, usually the latter, in 15 patients and have reversed papilledema in seven of these. Of eight patients treated prior to January, 1950, four survived longer than 30 months. Of seven patients treated since January, 1950, three were alive two and one-quarter years, one and one-half years and two years later. In four other patients, papilledema was not reversed by this dietary therapy. In the patients in whom papilledema was reversed, it was often several months before this improvement occurred.

One can not be certain in advance that the rice or low sodium diet will prove effective. Such diets can rarely be used if renal function is impaired to any important degree; also, if the diet is tried for several months but fails to reverse papilledema, serious irreversible deterioration may have occurred. In view of the newer, more effective methods of treatment, it would seem advisable to employ the low sodium diet as an adjunct rather than as the sole method of therapy in patients with malignant hypertension. Further, since a low sodium diet enhances the hypotensive effect of hexamethonium,¹⁷

it would seem desirable to employ the low sodium diet as a supplementary measure when this drug is used in treatment.

SYMPATHECTOMY

Several important reports on various technics of sympathectomy for the relief of malignant hypertension have appeared in the last decade. In 1944, Smithwick¹⁸ reported on 156 patients who had undergone radical lumbodorsal splanchnicectomy one to five years previously. Eighteen of the patients had preoperative papilledema. The 15 patients who were followed showed improvement. (Whether this meant disappearance of papilledema specifically was not stated, although two patients were said to have shown normal retinæ postoperatively.)

In 1948 Peet and Isberg¹² reported on 143 patients with malignant hypertension treated by splanchnic resection and followed for five or more years. The patients had severe neuroretinitis with papilledema measuring one diopter or more. In addition, the diastolic blood pressures were high and the course of the disease was rapidly progressive. The five year survival rate for the group was 21.6 per cent; the survival rate of the untreated patients reported by Keith and Wagener² was 1 per cent. Of the 60 patients with moderately or severely impaired renal function, none survived for five years. In the 115 patients in whom renal function was normal or only slightly impaired (urea clearance, 50 to 65 per cent; maximal specific gravity, 1.020 to 1.023 on a 48 hour concentration test), the five year survival rate was 30 per cent. From the figures given by Peet and Isberg,¹² we calculated that 28 patients had normal renal function, and that the five year survival rate in these patients was 70 per cent.

Thorpe and his associates¹⁹ analyzed 500 patients on whom sympathectomy was performed by Hinton, and found a three year survival rate of 44 per cent in 54 patients with preoperative papilledema.

Prior to January, 1950, bilateral radical lumbodorsal sympathectomies were performed on eight patients²⁰ in our group. The eighth patient, a 13 year old girl, died six hours after completion of the first stage. Brief histories of the remaining seven patients follow:

No. 26, a 21 year old male, was found to have grade IV (Keith-Wagener) retinæ on August 26, 1947. A two-stage sympathectomy was performed in September, 1947. Urinary excretion of phenolsulfonphthalein at the time of operation was 65 per cent in two hours; an Addis test showed a specific gravity of 1.014. The patient improved symptomatically after the operation; papilledema, hemorrhage and exudate receded for about seven months. K-W IV retinæ were again noted in April, 1948. The patient developed progressive renal failure and died in uremia on October 6, 1948, 14 months after diagnosis. At autopsy he was found to have had subacute glomerulonephritis.

No. 88, a 42 year old man, was found to have unilateral papilledema in December, 1946; by May, 1947, both optic discs were involved. Urinary excretion of phenolsulfonphthalein was 70 per cent in two hours. A two-stage sympathectomy was

performed in May, 1947. Upon examination six weeks and four months after the operation, the fundi were classified as K-W II. The patient died of a cerebrovascular accident on March 28, 1948, 16 months after a K-W IV classification of the retinae had been made.

No. 62, a 35 year old woman, was found to have K-W IV retinae in September, 1942. Urea clearance was 77 per cent; a routine urinalysis showed a specific gravity of 1.023. A bilateral lumbodorsal sympathectomy, performed in February, 1943, was followed by symptomatic improvement but no change in the papilledema. Sixteen months after operation papilledema was still present but hemorrhage and exudate had cleared. The patient was alive in November, 1944, 26 months after discovery of K-W IV retinae, but died some time thereafter.

No. 87, a 32 year old woman, was found to have unilateral papilledema in August, 1948. A sympathectomy was performed the same month. Urinary excretion of phenolsulfonphthalein was 100 per cent; specific gravity of the urine was 1.025 on admission to the hospital. The eyegrounds were classified as K-W II in May, 1949. The patient was alive and well in February, 1952, 43 months after diagnosis.

No. 89, a 19 year old man, was discovered to have papilledema in November, 1945; he was completely asymptomatic and had normal cardiac and renal function. A sympathectomy was performed in September, 1947, when evidence of cardiac failure and moderate renal damage appeared. Although the retinae improved and were reclassified as K-W II, the patient died of cardiac failure four months after operation and 27 months after diagnosis.

No. 96, a 31 year old male, had K-W IV retinitis in June, 1947, at which time a sympathectomy was performed. After the operation the specific gravity of the urine was 1.020. The blood pressure dropped considerably, and six months after the operation the retinae were classified as K-W II. The patient was alive and well in March, 1952, 57 months after diagnosis.

No. 101, a 23 year old Filipino male, developed a K-W IV retinitis while under observation in June, 1949. The specific gravity of the urine was 1.026. After one month of treatment in the hospital (bed-rest, 350 mg. sodium diet and intensive psychotherapy, which produced no improvement), a bilateral sympathectomy was performed in July and August, 1949. The papilledema disappeared within one month after operation and did not recur. The patient died suddenly on September 7, 1950, 15 months after diagnosis.

In six of these seven patients, reversal of papilledema occurred. In contrast to the usual course of the disease, death in uremia occurred in only one instance. This patient had subacute glomerulonephritis. The other deaths were due to cardiac or cerebral lesions. Two patients are living 43 and 57 months after diagnosis. The average survival of these seven patients was 28 months, in contrast to a survival of 8.4 months for the entire group, and of 16.3 months for the group of patients who were first seen at a time when renal function was normal or only slightly impaired.

Since January, 1950, sympathectomies have been performed on an additional four patients with malignant hypertension. Two patients showed temporary improvement and reversal of papilledema; one of these died of cardiac failure within the year, and the other died 22 months after surgery. Two patients had reversal of papilledema and were alive and well 23 months and six months following surgery.

It is apparent that sympathectomy in the early stages of malignant hypertension in patients with adequate renal function is an effective method of

treatment. Whether this measure is more effective than the newer sympatholytic drugs remains to be seen. The exact place of sympathectomy has not been established; since patients usually prefer medical to surgical treatment, trial of the hypotensive agents (discussed later) may well be preferable for initial therapy, while sympathectomy may be kept in reserve to be used if necessary.

PYROGENS

On the basis of the observation by Goldring and Chasis¹ that pyrogens produce renal vasodilatation and a fall in blood pressure, Page and Taylor¹³ gave patients with malignant hypertension frequent injections of Pyromen to produce fever four or more times a week. In his most recent publication, Page²¹ stated that in many cases the improvement was impressive, and that at present he believed pyrogen therapy to be the treatment of choice in malignant hypertension. He admitted that the treatment is harsh but considered it worth while from the standpoint that malignant hypertension itself "is more than harsh—it is lethal."

The only additional study of the pyrogens in malignant hypertension with which we are familiar is that by Kirkendall and January.²² These authors treated 14 patients, seven of whom had uremia at the beginning of therapy. Of the seven who did not have renal insufficiency, all died within 20 months of completion of therapy. Four of these patients showed subjective improvement and regression of retinopathy, but relapse occurred. Two of the seven patients with uremia were alive approximately two years after completion of therapy. The authors concluded that the benefits from bacterial pyrogen therapy were not outstanding, that the treatment was long and difficult to administer, and that the patients experienced considerable distress.

We have used pyrogen therapy in one patient. He developed angina pectoris as the temperature rose with each injection of Pyromen, although no clinical evidence of angina had existed previously. The therapy was discontinued when serial electrocardiograms indicated that he had had an acute myocardial infarction.

Considering the results effected by sympathectomy and the new hypotensive drugs, and in view of the work of Kirkendall and January,²² we cannot agree that pyrogen therapy is the treatment of choice in patients with adequate renal function. More work remains to be done with this method before Page's conclusion can be evaluated and a final judgment made.

ADRENALECTOMY

Bilateral adrenalectomy was first performed for malignant hypertension by Green²³ in a seriously ill patient. Spectacular clinical improvement occurred. His report stimulated a number of other investigators to study the problem. Their work was made more pertinent by the observations of

Selye²⁴ on the relationship between adrenal cortical hormones and salt in the experimental production of hypertension. The most recent investigation was presented by Merrill before the American College of Physicians.²⁵ He reported that satisfactory follow-up information was obtained on 15 of 18 patients who had been adrenalectomized. The indication for the operation was rapidly progressive vascular disease; 10 of the patients had evidence of nitrogen retention, and in all but two serious cardiac enlargement was apparent. Of the 15 patients, five were alive one year later; four of the five patients showed improvement in blood pressure and cardiac size. Of the 10 patients who died, myocardial infarction was the cause of death in two, ventricular arrhythmia in two, and renal insufficiency in four. Data on the effects of the operation on papilledema were not presented.

Considering the drastic nature of the operation, these results are not so encouraging as one would hope, even though patients who have undergone bilateral adrenalectomy can be kept alive indefinitely (it seems) by replacement therapy and the use of cortisone. It seems premature to advise this procedure unless other methods have failed, or until more data on its long-range benefits and hazards are available.

HYPOTENSIVE DRUGS

Prior to the past few years, when the newer hypotensive agents such as protoveratrine, hexamethonium and l-hydrazinophthalazine came into use, enthusiasm for most of the available hypotensive drugs was not great. The thiocyanates had fallen out of favor, partly because of their lack of effectiveness and partly because of the danger of toxic effects unless the blood concentrations were watched closely. Dibenamine was shown by Wunsch and associates²⁶ to have definite therapeutic benefit, but the drug had to be given by intravenous infusion, and important toxic symptoms occurred in almost all of their patients. The dihydrogenated ergot preparations,²⁷⁻³⁰ the cruder veratrum alkaloids^{27, 31} and Priscoline³² also have evoked little general enthusiasm, despite occasional favorable results, because of the unpredictable degree of hypotension and the high incidence of unpleasant side effects.^{27, 30, 31} Currens³³ and Meilman^{34, 35} recently demonstrated beneficial effects from protoveratrine; but their reported experience with malignant hypertension is not great, and they both emphasized that the range between the toxic and the therapeutic dose is narrow. Furthermore, Freis,³¹ who has reported on the veratrum preparations, dihydrocornine and hexamethonium, has found hexamethonium the most effective and least toxic of the drugs.*

Hexamethonium: A new wave of enthusiasm in the past four years followed the pharmacologic studies of Paton and Zaimis,^{36, 37} which showed that hexamethonium is a potent ganglionic blocking agent, effective in one-

* In a recent paper Hoobler and his associates^{38a} reported restoration of vision in malignant hypertension and relief of hypertensive headaches and encephalopathy with oral protoveratrine. They described three patients with hypertensive retinopathy as representative of their experience.

fifth of the dose of the tetraethylammonium compounds and active for hours instead of minutes. The most complete clinical studies on the use of hexamethonium in hypertension in man can be found in Smirk's papers.^{17, 38} In 150 patients with hypertension of varied etiology, Smirk and Alstad¹⁷ found that hexamethonium given parenterally was the most effective hypotensive agent with which they had had experience, and that the toxic effects were minimal when the drug was properly given under controlled conditions. They stated that papilledema either disappeared or was diminished in the 12 patients with malignant hypertension who were treated for two months or more. Freis and associates^{31, 39} confirmed Smirk's observations, and noted reversal of papilledema in 11 of 15 treated patients. Urecoline was used by Freis to alleviate the minor unpleasant side effects, such as dryness of the mouth, constipation and, at times, urinary retention, which are due to the parasympathetic blocking effect of hexamethonium.

The use of hexamethonium orally has not found such universal favor. Some of the early differences of opinion regarding the clinical value of hexamethonium have been due to the fact that the mode of administration has

TABLE I
Relationship of Initial Renal Function and Treatment
of Malignant Hypertension with Hexamethonium

Creatinine clearance (c.c./min.)	Number of cases	Reversal of papilledema	Survival to date (5 to 13 months)*
40-70	8	7	5
30-40	4	3	1
Less than 30	3	0	0

* With resumption of normal activity.

not received sufficient consideration. A number of British and Scandinavian reports⁴⁰⁻⁴² have demonstrated that hexamethonium is much more effective when given by the parenteral route. Kilpatrick and Smirk,³⁸ in a comparison of orally and parenterally administered hexamethonium, found that oral administration resulted in satisfactory control of hypertension in only one-fourth to one-third of patients who were well controlled by administration by the parenteral route. Schroeder in a recent paper⁴⁴ described excellent results in essential hypertension with oral hexamethonium followed by 1-hydrazinophthalazine. He stated that in 80 patients given this combined therapy, hypertension was completely controlled in all patients with benign hypertension and in all but two of 30 patients with malignant hypertension without renal insufficiency.

In our own experience^{44a} with the treatment of malignant hypertension with hexamethonium, we have relied solely on the subcutaneous route of administration. To date, adequate trial of this method of treatment in 17 patients with malignant hypertension has resulted in reversal of papilledema and clinical improvement in 10. The follow-up has been short (from five

to 13 months), but the patients are being observed frequently. The relationship between the renal function of 15 of these patients and the results of hexamethonium therapy is illustrated in table 1. Of the 10 patients whose papilledema was reversed, only three had creatinine clearances exceeding 50 c.c. per minute, and all of the clearances were under 70 c.c. per minute. It is of interest that the group of patients whose papilledema reversed included two patients with chronic glomerulonephritis and two with chronic pyelonephritis; in these four patients the creatinine clearances were between 33 and 57 c.c. per minute prior to therapy. In those patients whose creatinine clearances were less than 30 c.c. per minute, renal failure progressed despite

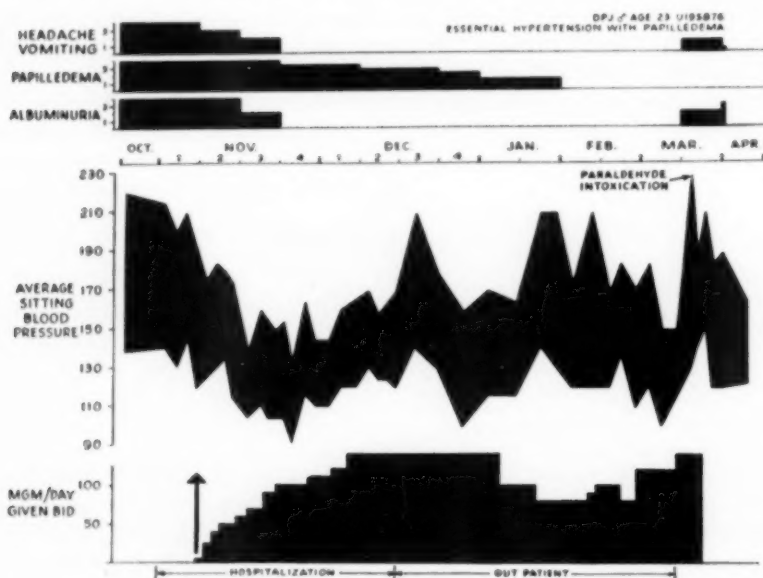


FIG. 1. D. P. J., male, age 23. Essential hypertension with papilledema. Hexamethonium treatment of malignant hypertension.

hexamethonium therapy. Three cases illustrating the value of hexamethonium follow:

No. 117, a 23 year old male, was first seen in November, 1951, because of severe headaches and episodes of vomiting during the preceding two months, associated with anorexia, nervousness and weight loss of a year's duration. He had a past history of what was probably acute pyelonephritis four months prior to entry, although a urologic study showed no abnormalities except for trigonitis. Examination revealed a severely ill man with a blood pressure of 210/135 mm. of Hg, whose fundi revealed papilledema with multiple hemorrhages and exudates and a decrease in visual acuity so severe that he could not recognize members of his family. The laboratory data revealed urinary excretion of 6 gm. of albumin per 24 hours, creatinine clearance

of 66 c.c. per minute, and nonprotein nitrogen of 40 mg. per cent. The electrocardiogram revealed left ventricular hypertrophy.

The patient was treated for four days in the hospital with parenteral fluids, sedation and Demerol, but despite this medication continued to suffer from severe headaches, projectile vomiting and further loss of vision. Hexamethonium therapy was begun on November 6, 1951, and the dosage was progressively increased (figure 1). Within 48 hours vomiting ceased and headaches improved; within four days, the patient had a voracious appetite. Within three weeks he was essentially free of headaches, was eating and sleeping well, required no analgesics and was ambulatory; his vision had begun to improve, and his blood pressure had decreased to 180-160/110-120 mm. of Hg. By February 1, 1952, his fundi were classified as K-W II, and his vision had improved from the original 20-100 in the left eye and 20-50 in the right eye to 20-20 and 20-30, respectively. At the same time (in February), creatinine clearance increased to 91 c.c. per minute, the urine became free of albumin, the abnormalities of the sediment disappeared and the electrocardiogram revealed significant T wave changes toward the normal (figure 2).

He has been seen frequently since that time, and his renal function tests are now essentially normal. The urine occasionally shows slight albuminuria, the creatinine clearance is 83 c.c. per minute, and the phenolsulfonphthalein excretion is 25 per cent in 15 minutes.*

Comment: The rapid improvement in vision, relief of nausea and vomiting, and the more gradual improvement in papilledema were dramatic. The disappearance of albuminuria too was a phenomenon that rarely occurs spontaneously.

No. 108, a 29 year old male, was seen on July 23, 1951, because of failing vision and headaches. He had had known chronic glomerulonephritis since the age of 17. Physical examination revealed a blood pressure of 250/160 mm. of Hg, papilledema, hemorrhages and exudates in the fundi, and slight edema of the ankles. Laboratory data revealed a creatinine clearance of 43 c.c. per minute and a serum creatinine of 2.6 mg. per cent; 6 gm. of protein were excreted in 24 hours in the urine; the non-protein nitrogen was 15 mg. per cent. The electrocardiogram revealed left ventricular hypertrophy.

Treatment for two or three weeks consisted of bed-rest, sedation and a 500 mg. sodium diet. During this period the headaches and vomiting were slightly ameliorated, but the patient was unable to eat and appeared quite ill. Hexamethonium, by subcutaneous injection, was begun on August 17, with progressively increasing doses (figure 3). Within a few days headaches, vomiting and vision began to improve; within a week striking improvement had occurred. Papilledema progressively subsided and had disappeared completely by September 18. The patient was then discharged from the hospital but has continued to take hexamethonium by self-administered subcutaneous injection.

He has been seen frequently since that time. The creatinine clearance on June 11, 1952, was 27 (uncorrected), and the serum creatinine was 3.1 mg. per cent. He was free of papilledema, and his blood pressure was 275-300/175 mm. of Hg.†

* The patient was last seen on March 4, 1953 (follow-up of 16 months), at which time the blood pressure was 180/120 mm. of Hg, the fundi were K-W II, and the patient was asymptomatic.

† Since this paper was written, the patient's renal function has slowly deteriorated. In October, 1952, the serum creatinine was 6.5 mg. per cent and the creatinine clearance was 12.8 c.c. per minute. He developed cerebrovascular symptoms, and it appeared that he was not going to survive. There was no papilledema, hemorrhages or soft exudates at this time.

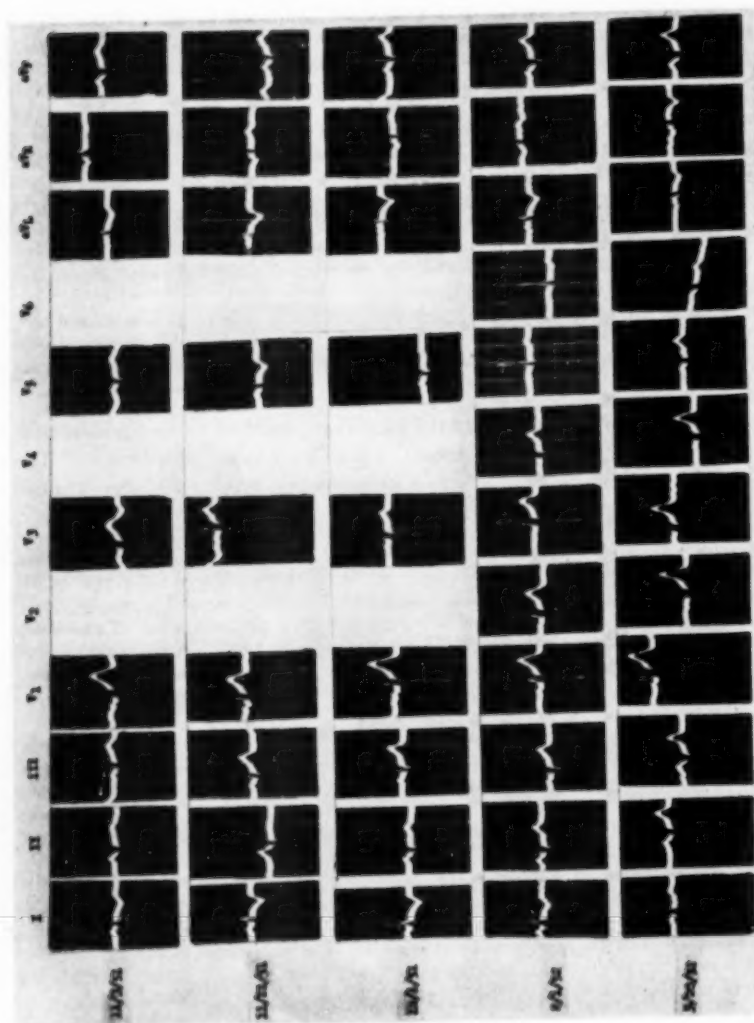


FIG. 2. D. P. J., male, age 23. Malignant hypertension (essential). Hexamethonium therapy begun 11/6/51. 70 mg. b.i.d. on 3/20/52.

Comment: The history of this patient illustrates the fact that, despite severe impairment of renal function and the presence of underlying chronic renal disease, reversal of the accelerated phase of the disease can occur and the condition of the patient can be restored to the premalignant state for at least a year. Renal function, however, may remain poor and over a period of months may slowly become worse, so that death in uremia may occur despite the initial improvement and despite the fact that papilledema remained absent.

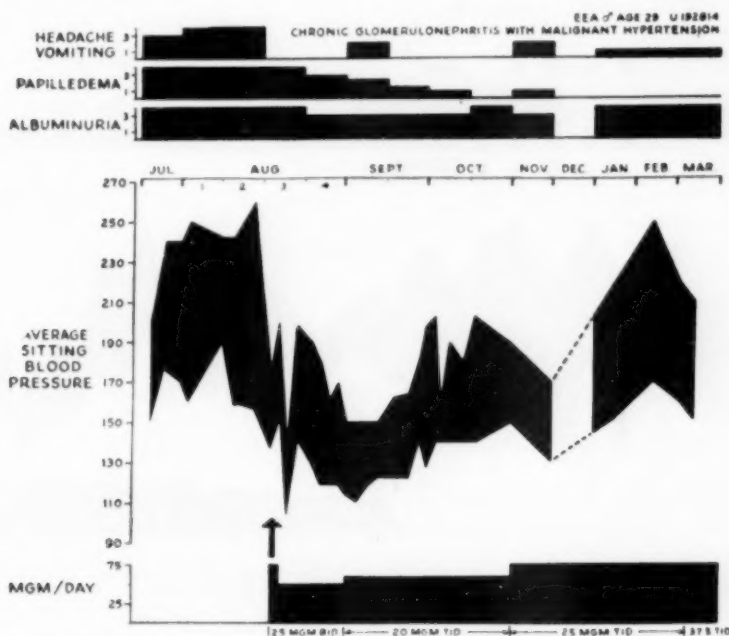


FIG. 3. E. E. A., male, age 29. Chronic glomerulonephritis with malignant hypertension. Hexamethonium treatment of malignant hypertension.

No. 115, a 30 year old male, was found to have hypertension in 1948. In 1950 bilateral hydronephrosis and pyelonephritis, secondary to congenital stricture of the bladder neck and benign hypertrophy of the prostate, were discovered. After a transurethral resection, lower nephron nephrosis occurred, which improved with treatment. In February, 1951, his blood pressure was 230/150 mm. of Hg, the fundi were classified as K-W II, he had moderate albuminuria, and the blood urea nitrogen was 13 mg. per cent. He developed congestive failure and blurred vision in the left eye in June, 1951. At this time the fundi showed papilledema, hemorrhages and exudates, and the blood urea nitrogen was 16 mg. per cent.

He was treated with veratrum and digitalis, which improved the cardiac symptoms but not the papilledema. Nausea, vomiting and headaches also were benefited by therapy. In June, 1951, the symptoms recurred despite the continued use of

veratrum. The patient was re-admitted to the Southern Pacific Hospital because of dyspnea and vomiting; congestive heart failure had increased.* For the next month, despite a 250 mg. sodium diet, digitalis and carboresins, cardiac failure continued, papilledema remained, and the patient developed pulmonary edema. His heart increased in size, the blood pressure ranged from 200-250/135-155 mm. of Hg, and the serum creatinine was 3.4 mg. per cent.

Hexamethonium therapy was started on September 25, 1951, and the dose was progressively increased (figure 4). He improved rapidly and on October 15 (three weeks later) was completely asymptomatic and showed no evidence of heart failure. Within three weeks his vision had improved from 20-30 and 20-40 to 20-20 and 20-15, and the papilledema had disappeared.

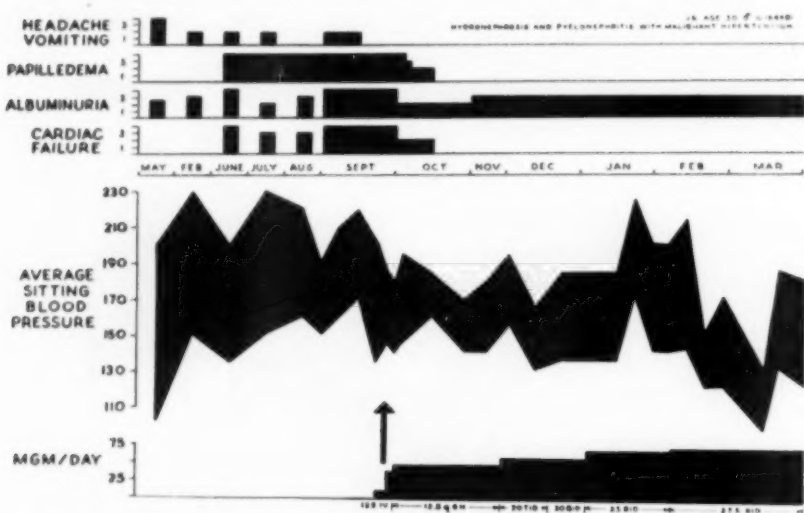


FIG. 4. J. G., male, age 30. Hydronephrosis and pyelonephritis with malignant hypertension. Hexamethonium treatment of malignant hypertension.

He has been examined frequently in the Out-Patient Department of the University of California Hospital. When he was last seen the blood urea nitrogen was 22.8 mg. per cent and the average blood pressure was 160/120 mm. of Hg. He has remained completely asymptomatic, and returned to work on April 7, 1952. Despite a full-time job, he has no dyspnea or other cardiac symptoms; he is on a normal diet and is receiving no medication other than hexamethonium.†

Comment: In this case the improvement was spectacular, since the patient was desperately ill with cardiac and renal failure, had almost complete loss of vision, and had failed to respond to all other forms of therapy. Twelve months later he was asymptomatic, and the only medication he was receiving

* We are grateful to Dr. Bernard Kaufman, Jr. for the details of this patient's hospitalization at the Southern Pacific Hospital in San Francisco during the early stages of his disease.

† The patient was last seen on March 3, 1953 (follow-up of 18 months), at which time he had no complaints and was working full time.

was hexamethonium. He had returned to work and stated that he felt about as well as at any time in his life.

L-Hydrazinophthalazine: The most recent addition to the hypotensive armamentarium has been l-hydrazinophthalazine.^{45, 46} Schroeder in a later report⁴⁴ indicated that, while l-hydrazinophthalazine given orally is often effective, hexamethonium is more so, and that patients with hypertension should be given hexamethonium first, then l-hydrazinophthalazine should be added. Johnson, Freis and Schnaper⁴⁷ noted that the results with l-hydrazinophthalazine alone are not striking; sustained hypotensive effects were found in only three of their 17 patients while they were under treatment with l-hydrazinophthalazine alone. Toxic effects included severe headache (which in four cases necessitated cessation of the drug), tachycardia, dizziness, weakness, nausea and vomiting. These last symptoms were rarely serious. The side effects were most likely to be associated with doses of the drug which produced a profound hypotension. The authors combined l-hydrazinophthalazine with a variety of other hypotensive agents and concluded that the drug was probably of greatest value when alternated with hexamethonium. This view is shared by a number of other investigators, who believe that the combination of hexamethonium and l-hydrazinophthalazine is synergistic. Schroeder⁴⁴ stated that in ordinary hypertension the combination will return the blood pressure to approximately normal levels in practically all cases. He warned that the drug should be given only by physicians skilled in its use, that patients should be hospitalized for the introduction of therapy, and that the dose should be increased very gradually. His data on malignant hypertension were most encouraging, but insufficient details were given.

In our own experience, we have had two patients with malignant hypertension in whom the addition of oral l-hydrazinophthalazine was of striking benefit after only modest improvement resulted from parenterally administered hexamethonium. In one patient, the blood pressure was restored almost to normal when 300 mg. daily of l-hydrazinophthalazine orally were added to 70 mg. of hexamethonium twice daily subcutaneously. In a second patient, in whom postural hypertension persisted after treatment with hexamethonium given subcutaneously, l-hydrazinophthalazine, at first in combination and then alone, resulted in a decrease in the blood pressure to almost normal levels and subsequent reversal of papilledema.

DISCUSSION

It is apparent that the outlook for the patient with malignant hypertension is considerably brighter than it was five years ago. The physician has at his disposal a variety of therapeutic methods which will reverse the papilledema and improve the clinical state at least temporarily in approximately half the patients, although the ultimate benefit from treatment remains to be

seen. Thoracolumbar sympathectomy appears to be the most successful surgical procedure, although bilateral adrenalectomy may assume a greater rôle as experience accumulates. Hexamethonium and 1-hydrazinophthalazine are the most effective drugs, while repeated pyrogen therapy is considered by Page²¹ to be the most effective form of therapy. The newer purified preparations of Veratrum are also effective agents.

In our own experience with hexamethonium therapy, papilledema was reversed and significant clinical improvement has resulted in 40 to 50 per cent of our patients. The experience is still limited and the follow-up period is short. More time is needed before final conclusions can be made regarding increased survival, the most effective form of therapy and, in the case of the newer drugs, the most desirable mode of administration and the duration of therapy.

One of the unanswered problems in the treatment of patients with malignant hypertension is the proper management following the initial reversal of papilledema with hexamethonium. In most patients some tolerance to the drug occurs. The patient may then have a blood pressure which, while perhaps not so high as before treatment, is considerably higher than that achieved during hospitalization. In three of our patients in whom reversal of papilledema and significant temporary improvement occurred, the blood pressure rose to almost pre-treatment levels and renal failure slowly progressed, with ultimate death in uremia in two of these patients and in cardiac failure in one. In this last patient, hexamethonium was changed from subcutaneous to oral administration after the patient left the hospital, because the patient's coöperation and mentation were such that it was believed unwise to trust him with self-injection. This patient died in cardiac failure and not in uremia; at the time of death, the creatinine clearance was 35 c.c. per minute, and the serum creatinine was 2.0 mg. per cent.

The question that arises is whether much larger doses of hexamethonium should be employed as tolerance develops, or whether the renal and coronary arteriolar lesions have become so far advanced that complete reversal cannot be achieved; in view of the difficulties of continued parenteral injections and the need for higher dosage, perhaps hexamethonium should be stopped after the malignant phase has been reversed. Whether the addition of 1-hydrazinophthalazine, higher doses of hexamethonium, or sympathectomy should be employed after the papilledema has been reversed remains to be decided after more experience has been gained.

Treatment with hexamethonium should be instituted only when the patient is hospitalized, under careful medical supervision. The initial dose should be small, 2 to 5 mg. injected subcutaneously; it should be increased gradually, depending upon the response of the patient, until effective doses have been reached. The postural effects of the drug must be appreciated and used, both to prevent toxic effects from the marked postural hypotension that occurs for one to several hours after an injection, and for therapeutic

purposes, to maintain a hypotensive effect after the blood pressure is no longer reduced in the recumbent position. Because of individual variation in response the patient must be watched closely, particularly during the first week of therapy, when even small doses may produce alarming hypotensive reactions. The patient should be warned about the symptoms of hypotension and advised to lie down when they occur. It is also wise to anticipate the possible symptoms due to blocking of the parasympathetic impulses (such as dryness of the mouth and constipation) and, if they occur, to use such drugs as Urecoline or neostigmine. In one of our patients, hexamethonium had to be discontinued because of paralytic ileus; this complication was also noted by Freis³¹ and Mackey and Shaw.⁴⁶

Contraindications to the use of hexamethonium are not clearly defined at the present time. Sudden hypotension in the presence of severe arteriosclerosis of the cerebral, coronary or renal arteries may result in abrupt reduction in blood flow and may induce thrombosis. These complications have been reported, but fortunately they are rare and in our experience have not occurred. Reduction of the blood pressure to levels of approximately 180–190 mm. of Hg systolic for the first few days, then to 150–160 mm. of Hg for the next few days, and not attempting to reduce the blood pressure to below 140 for at least a week, may reduce the likelihood of thrombosis. We found that patients who had a blood pressure of 250/150 mm. of Hg when first seen might develop dizziness and faintness; in one patient, numbness and paresthesia of an arm and hand occurred when the blood pressure was reduced in the first few days to 140/90 mm. of Hg. Two or three weeks later this reduction of blood pressure could be obtained without untoward symptoms. It appears, therefore, that it may take a week or two to adjust the older patient to a lower range of blood pressure.

Studies of the renal hemodynamics⁴⁸ during administration of hexamethonium demonstrated that the early hypotensive period is characterized by a decrease in renal blood flow, glomerular filtration rate and filtration fraction, accompanied by moderate oliguria. The fear of producing renal failure has been emphasized, particularly by Grob and his associates.⁴⁹ The physician must take this risk if the patient has impaired renal function and papilledema because, if treatment is not given, experience indicates that such a patient has little likelihood of surviving. The combination of 1-hydrazinophthalazine, which increases the renal blood flow,^{31, 44, 45, 47} and hexamethonium may prove to be the most desirable therapy for patients with impaired renal function. Not all investigators agree that hexamethonium causes a decrease in the renal blood flow; in fact, Kirkendall and Culbertson⁵⁰ showed that occasionally the renal blood flow increased after hexamethonium was injected intravenously. Smirk and Alstad¹⁷ in a report on the use of this drug, stated: "In no case was effective blood pressure reduction associated with rise in the nonprotein nitrogen or with symptomatic induction of impairment in the excretory functions of the kidney."

In our experience, when hexamethonium was given to patients with advanced renal insufficiency (creatinine clearance less than 30 c.c. per minute), reversal of the renal failure did not occur, possibly because the drug was given too late in the course of the disease. Of seven patients in whom renal function was significantly impaired (creatinine clearance less than 50 c.c. per minute), but who showed no clinical evidence of uremia, the malignant phase was reversed in five without adverse effect on the renal function; in two, renal failure progressed even after the papilledema had been reversed. In some cases, however, the renal function improved; and in a number of instances albuminuria, hematuria and excretion of casts have either greatly decreased or disappeared as the blood pressure decreased after administration of hexamethonium. The disappearance or significant reduction of albuminuria in four cases (figure 1) indicates that the reduction in blood pressure following treatment with hexamethonium has a favorable effect on the arteriolar vasoconstriction and glomerular damage.

CONCLUSIONS

1. The prognosis of malignant hypertension is no longer hopeless with modern therapy, particularly if treatment is instituted prior to the stage of severe renal impairment.
2. Treatment of malignant hypertension should be instituted promptly after adequate investigation has excluded the presence of reversible conditions such as pheochromocytoma and unilateral atrophic pyelonephritis.
3. The most effective medical management at the present time appears to be the use of hexamethonium by parenteral injection, combined with the oral use of 1-hydrazinophthalazine, low sodium diet and adequate attention to the emotional needs of the patient. The newer veratrum alkaloids, such as protoveratrine, are also of value.
4. A combination of hexamethonium given orally and 1-hydrazinophthalazine may prove to be as effective as the combination suggested in point 3 above, but, in view of the work of Kilpatrick and Smirk,²⁸ this remains to be proved.
5. When the new antihypertensive agents are used the patient should be under close medical supervision (preferably in the hospital) when the treatment is initiated, and great care should be exercised to avoid hypotensive reactions.
6. Sympathectomy is an effective form of therapy for malignant hypertension in the presence of normal renal function; the accelerated phase is reversed in 30 to 50 per cent of patients.

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MALIGNANT HYPERTENSION ASSOCIATED WITH UNILATERAL RENAL ARTERY OCCLUSION: THREE CASES *

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THE elucidation of the rôle played by renal ischemia in the pathogenesis of hypertension by Goldblatt's now classic experiments^{1, 2, 3} has constituted one of the most significant recent advances in this field. With the accumulation of such distinct experimental evidence it was natural that efforts should follow to determine the possible relationship of renal ischemia to clinical hypertension as seen in man.⁴ In general, such studies have indicated that only in relatively isolated instances can a Goldblatt mechanism be definitely incriminated. The difficulties and hazards inherent in translating experimental data to clinical medicine are magnified when the problem is as complex as that of hypertension. Nevertheless, it has become apparent that a true Goldblatt mechanism may be operative in certain patients with hypertension and that in such instances surgery may produce dramatic results. The occurrence of a "Goldblatt kidney" has therefore become of more than academic interest, and for this reason the following cases are presented.

CASE REPORTS

Case 1. Clinical History: On July 29, 1946, a 44 year old white man was admitted to the medical service of Grasslands Hospital, Valhalla, N. Y., with chief complaints of headache and bilateral pedal edema. He had been in usual good health until six days prior to hospitalization when, after a drinking bout, he awoke with a dull aching pain in the frontal region and noted puffiness of his cheeks, eyelids and ankles. In addition, progressively increasing exertional dyspnea had developed in this interval, never having previously occurred. Further anamnestic elements were unremarkable except that the patient had noted diurnal urinary frequency.

Physical examination disclosed a moderately obese, 44 year old white man in no discomfort. Oral temperature was 98.6° F.; pulse, 84/minute; respirations, 20/minute. The blood pressure was 200/110 mm. of Hg. The eyelids and cheeks were puffy. The ocular fundi were not unusual. Rhonchi were heard throughout both lung fields but the heart was unremarkable. The anterior liver edge was palpated three fingerbreadths below the right costal margin. Bilateral costovertebral angle tenderness was elicited. There was 4 plus pitting edema of the feet and ankles and 1 plus pitting edema of the legs and sacral area.

Admission urinalysis showed a specific gravity of 1.010, with 4 plus albumin and numerous red blood cells. This, with other laboratory data, suggested the diagnosis of an acute exacerbation of chronic glomerulonephritis. During the initial fortnight of hospitalization the non-protein nitrogen rose steadily to a peak of 120 mg.

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per cent. For the first few days the urinary output was poor, but it gradually increased to normal. In spite of this, the edema was essentially unaltered and even appeared to progress slightly. Attempts to induce diuresis by all available means, including mercurial derivatives and digitalis, were unsuccessful. Abdominal paracenteses were performed on October 19, October 27 and November 3, with the recovery of copious amounts of ascitic fluid. The non-protein nitrogen level in the meanwhile had declined to 30 mg. per cent, and the urinary output continued to improve, the average daily amount early in November being 2,800 c.c. On November 15 the patient's course was complicated by a perforated, bleeding peptic ulcer. The blood pressure, which previously had been 220/110 mm. of Hg, fell to 120/70 mm. of Hg. Laparotomy was performed and a perforation along the lesser curvature of the stomach was closed. The postoperative course was remarkably benign. However, the gross and widespread edema persisted and was refractory to all the diuretic methods which had been employed. In the middle of January, 1947, it was decided that an additional trial of Mercupurin was warranted. On this occasion successful diuresis was achieved, and within a five day period a loss in body weight of 25 pounds was recorded. The edema disappeared and the patient was remarkably improved; this was reflected in the laboratory data, which showed a sharp increase in the blood total protein as well as a diminution in the excreted urinary albumin, which had declined from 7 gm./100 c.c. of urine on admission to 0.156 gm./L.

During hospitalization the urine had consistently shown a low specific gravity, negative glucose, 4 plus albumin and numerous red blood cells. In February the number of erythrocytes in the urine declined, and in March all hematuria ceased. Urinalysis at the time of discharge on April 2 showed a specific gravity of 1.008, acid reaction, negative glucose, 3 plus albumin, occasional leukocytes, a few granular casts and no red blood cells. Final diagnoses were chronic glomerulonephritis and gastric ulcer with perforation (surgically repaired).

On October 7, 1947, the patient was re-admitted to Grasslands Hospital for repair of a ventral hernia which had developed at the site of laparotomy. Blood pressure on admission was 170/105 mm. of Hg. On October 8 the non-protein nitrogen was 48 mg. per cent, and on October 20 it was 42 mg. per cent. Serial urinalyses showed a specific gravity ranging from 1.012 to 1.019, albuminuria varying from a faint trace to 2 plus, and consistently negative glucose. The urinary sediment contained pus cells on several examinations but no red blood cells at any time. On October 15 a ventral herniorrhaphy was performed, and the patient was discharged 10 days later after an uneventful postoperative course.

The state of general health was good until early 1950, when headaches, increasing dyspnea and weight loss prompted hospitalization. On April 28 he was therefore admitted to V Medical Service, Boston City Hospital. Blood pressure on entry was 270/160 mm. of Hg. Moderate generalized arteriolar narrowing was noted on fundoscopic examination. Scattered pulmonary râles were ausculted bilaterally, but the heart was unremarkable except for moderate enlargement. The liver was palpated four fingerbreadths below the right costal margin. Urinalysis showed a specific gravity of 1.010, with 1 plus albumin and no red blood cells in the sediment. A chest x-ray revealed an increased transverse cardiac diameter and obliteration of the right costophrenic angle. Roentgenogram of the abdomen disclosed the liver at the level of the right iliac crest; the left kidney was normal in size, shape and position, while that on the right was obscured. Initial therapy was directed at alleviating the asthmatic dyspnea and improving the general condition. At 11:30 p.m. on May 2, after complaining of extreme restlessness and shortness of breath for approximately 30 minutes, the patient suddenly lapsed into unconsciousness, becoming unresponsive to questioning and noxious stimuli. He was intensely cyanotic and respirations were irregular, although the pulse continued strong. Repeated tonic contractions of the



FIG. 1. *Case 1.* Gross specimen, showing contracted right kidney and right renal artery thrombus. Latter is evident as occluding mass extending from ostium of opened renal artery toward hilum of kidney.

entire body were observed during the 20 minute period immediately following the onset of coma, but these did not persist. A lumbar puncture yielded grossly bloody spinal fluid. The coma became progressively deeper, and approximately eight hours after it had supervened the patient died.

Pathology: Autopsy, performed six hours post mortem, disclosed the immediate cause of death to have been a massive pontine hemorrhage. Apart from this, cardiomegaly and congestive hepatomegaly, the pertinent findings were restricted to the kidneys and these will be described in detail.

Grossly the organs were asymmetrical, the right being the smaller and weighing 85 gm., the left weighing 125 gm. (figure 1). On the right the capsule stripped with increased resistance from a diffusely and coarsely granular reddish brown surface. On section there was seen to be relatively good corticomedullary differentiation, although the width of the cortex was diminished, measuring 3 to 4 mm. The pyramids were not remarkable. On the left the capsule stripped with similarly increased resistance from a pale, yellow-brown, coarsely granular surface which was free of petechiae. Section disclosed good corticomedullary differentiation, with a wider band of measurable cortex than in the contralateral organ, the width being 6 to 8 mm. A diffuse pale yellow streaking was apparent on the cut surface and was particularly prominent in the pyramids. Calyces, pelves and ureters were unremarkable bilaterally. Peripelvic fat appeared slightly increased. On the right the renal artery was almost completely occluded for a distance of 1 cm. from its ostium by an adherent, firm, reddish yellow clot. The left renal artery was patent throughout its course.

On microscopic examination the capsule of the right kidney was unremarkable. The stroma in general appeared compact, suggesting atrophy. The majority of the glomeruli were intact but slightly swollen and presented somewhat thickened capsules. However, numerous glomeruli were completely or partially obliterated, being replaced by hyaline eosinophilic material. Tubules in many areas, especially beneath the renal capsule, were dilated and exhibited swollen epithelial cells. Rarer small homogeneous eosinophilic tubular casts were noted. The interstitial tissue contained numerous chronic inflammatory cells, chiefly lymphocytes. Arterioles showed moderate to marked subendothelial proliferation, and vessels were moderately engorged throughout.

On the left the capsule was not unusual. Glomeruli in general were intact, although apparently swollen; however, many were fibrosed and others showed capsular adhesions. Alternative glomerulitis was noted occasionally. Tubules were markedly dilated, especially beneath the renal capsule, and occasionally contained large eosinophilic colloid casts. The interstitial tissue appeared of increased cellularity, with a dense infiltrate of chronic inflammatory cells, chiefly lymphocytes. Arterioles showed moderate subendothelial thickening, with a suggestion of "onion-peeling." Rare foci of necrotizing arteriolitis (figure 2) were noted.

Section of the right renal artery (figure 3) showed a large subendothelial zone of amorphous, acellular ground substance, with numerous cholesterol clefts and scattered calcium particles, surrounding a central organized and organizing thrombus. The latter therefore appeared to have developed at the site of an atheromatous plaque. Sections of other tissues, including pancreas and liver, presented hyperplastic arteriosclerosis resembling that in the right kidney, as described above.

The microscopic diagnosis was benign nephrosclerosis of the right kidney, benign and malignant nephrosclerosis of the left kidney, and occluding thrombus of the right renal artery.

Summary: This 47 year old white man had been in usual good health until the age of 44, when the seemingly acute development of severe hypertension and associated urinary findings led to a diagnosis of recurrent acute glomerulonephritis. Data relative to the state of the blood pressure prior

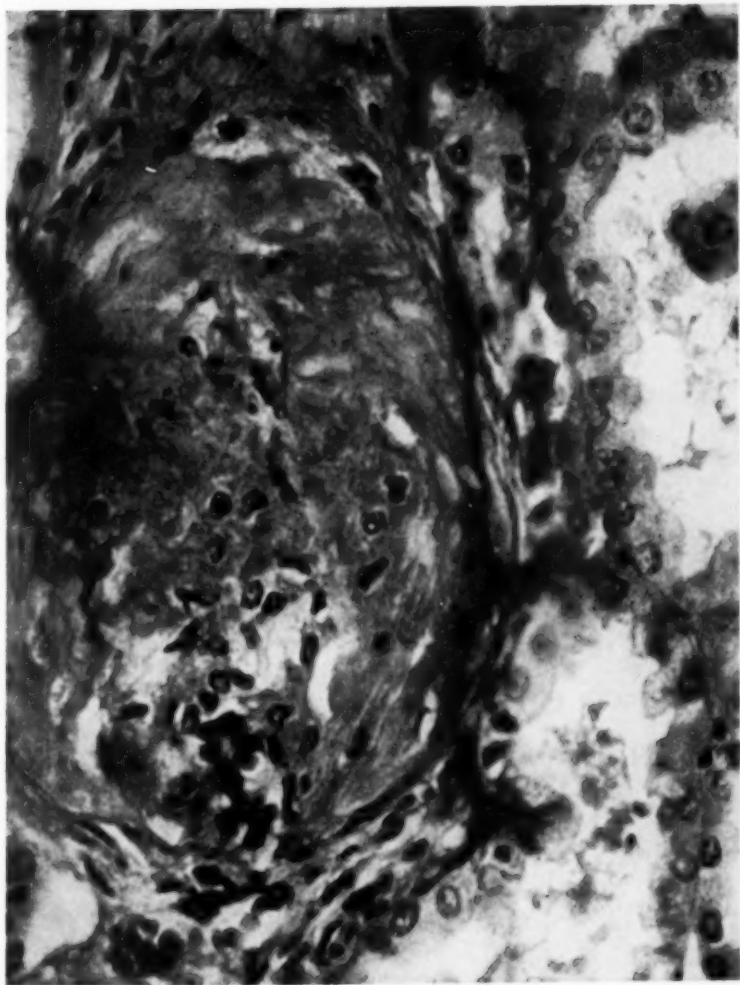


FIG. 2. Case 1. Photomicrograph of left kidney, demonstrating hyperplastic arteriolitis and necrosis consistent with malignant nephrosclerosis. (Hematoxylin and eosin, $\times 800$.)

to this unfortunately are not available. The hematuria regressed and did not recur, but the blood pressure remained elevated. The finding of almost complete thrombotic occlusion of the right renal artery at autopsy three years later suggests that the acute initial clinical picture was on this basis. Death resulted from massive pontine hemorrhage. Histopathologic study disclosed the characteristic lesions of benign and malignant nephrosclerosis in



FIG. 3. *Case 1.* Low power view of right renal artery with thrombus situated at upper aspect of photomicrograph and arterial wall inferiorly. Calcium deposits in wall of artery are evident as dark flecks. (Hematoxylin and eosin, $\times 80$.)

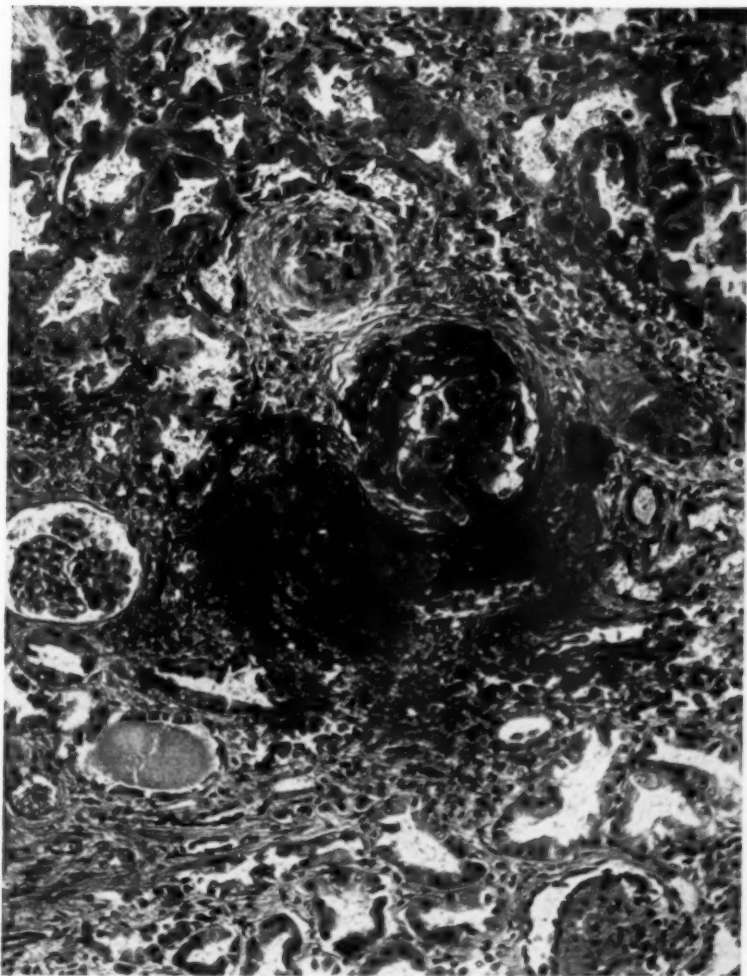


FIG. 4. Case 2. Photomicrograph of right kidney, showing hemorrhage, glomerular changes and necrotizing arteriolitis. (Phloxine-methylene blue, $\times 200$.)

the kidney with intact blood supply, while the right kidney, the renal artery of which was almost completely thrombosed, was spared such changes and exhibited findings consistent with merely the benign form of nephrosclerosis.

Case 2. Clinical History: A 59 year old white man was admitted to IV Medical Service, Boston City Hospital, on December 26, 1943, with a vague history of leg pain of four days' duration. The patient was an unreliable informant but stated that he had noted dyspnea on exertion for several years. Daily oral digitalis had been in-

stituted and continued since an episode of ankle edema three years prior to admission. During the previous three months severe frontal headaches had occurred. The remainder of the history was unremarkable.

Physical examination disclosed an emaciated and somnolent, elderly appearing white man in no acute distress. The blood pressure was 220/150 mm. of Hg. The ocular fundi were unremarkable. The heart was enlarged but free of murmurs. Breath sounds were diminished over the left pulmonary base posteriorly.

Urine on admission was yellow and acid, with a specific gravity of 1.003, negative albumin and negative glucose; the sediment contained occasional leukocytes, 4 to 6 red blood cells per high power field, and no casts. Non-protein nitrogen was 51 mg. per cent. A chest x-ray on the day after entry showed extensive calcification of the pleura on the right and chronic fibrous tuberculosis at the right pulmonary apex. The prime pathologic process was considered to be essential hypertension, and therapy consisted of a low-sodium diet, digitalis and diuretics. The patient was mentally and physically sluggish throughout the hospital course. On the evening of December 30, acute pulmonary edema developed and was treated with tourniquets, venesection and sedation. The patient did not respond and died shortly afterward on the fourth hospital day.

Pathology: Autopsy (Dr. Stanley L. Robbins), performed eight hours post mortem, revealed multiple small cerebral hemorrhages, cardiomegaly, bilateral bronchopneumonia and pulmonary edema, fibrous tuberculosis of the right pulmonary apex, and right obliterative calcific pleuritis. The only remaining pertinent findings were renal and these will be presented in detail.

The left kidney was greatly reduced in size, weighing 25 gm. The capsule was thickened and stripped readily, exposing a dark red, granular surface. A vesicle containing light brown fluid was seen near the upper pole. Section encountered normal resistance, disclosing a reddish cut surface on which the architecture was clearly discernible. The pyramids were extremely dark. The calyces, pelvis and ureter were unremarkable. The right kidney weighed 120 gm. The capsule stripped with increased difficulty from a coarsely granular surface. Section encountered increased resistance and disclosed normal color and architecture. The pyramids were somewhat pale. The calyces, pelvis and ureter were negative. The left renal artery presented several raised plaques on its intimal aspect, and at a distance of approximately 1 cm. from the aortic ostium was almost completely occluded by a dense, adherent, reddish yellow thrombus. The right renal artery was not unusual except for several small atheromatous plaques.

Microscopic examination of the left kidney showed marked congestion and a ragged subcapsular outline. Many glomeruli exhibited increased cellularity, congestion and hyaline vascular changes. Several fibrotic glomeruli were noted in addition. The arterioles in general showed thickened hyalinized walls. The interstitial tissue was increased throughout. The tubules in the cortex appeared compressed. Lymphocytic infiltrations were present in wide areas. The renal pelvis was not remarkable.

Section of the right kidney disclosed glomeruli similar to those on the left, but also presented occasional fibrinous and hemorrhagic lesions (figure 4). The interstitial tissue was increased and lymphocytic infiltrates were present in many areas. The arterioles everywhere showed thickened hyalinized walls and occasionally exhibited an increase in thickness of the media, with concentrically arranged nuclei and fibrinous collections (figure 5). Tubules in the region of the cortex resembled those on the left. The renal pelvis was free of change.

Section of the left renal artery (figure 6) showed small spaces within its wall containing refringent material suggesting cholesterol and indicating an underlying

atheroma. Almost completely occluding the lumen was a mass of vascularized connective tissue with concentric lamellae and areas of calcification. In addition, hyperplastic arteriolar sclerosis of varying degree was observed in sections of many other organs.

The microscopic diagnosis was benign and malignant nephrosclerosis of the right kidney, benign nephrosclerosis of the left kidney, and thrombosis of the left renal artery.

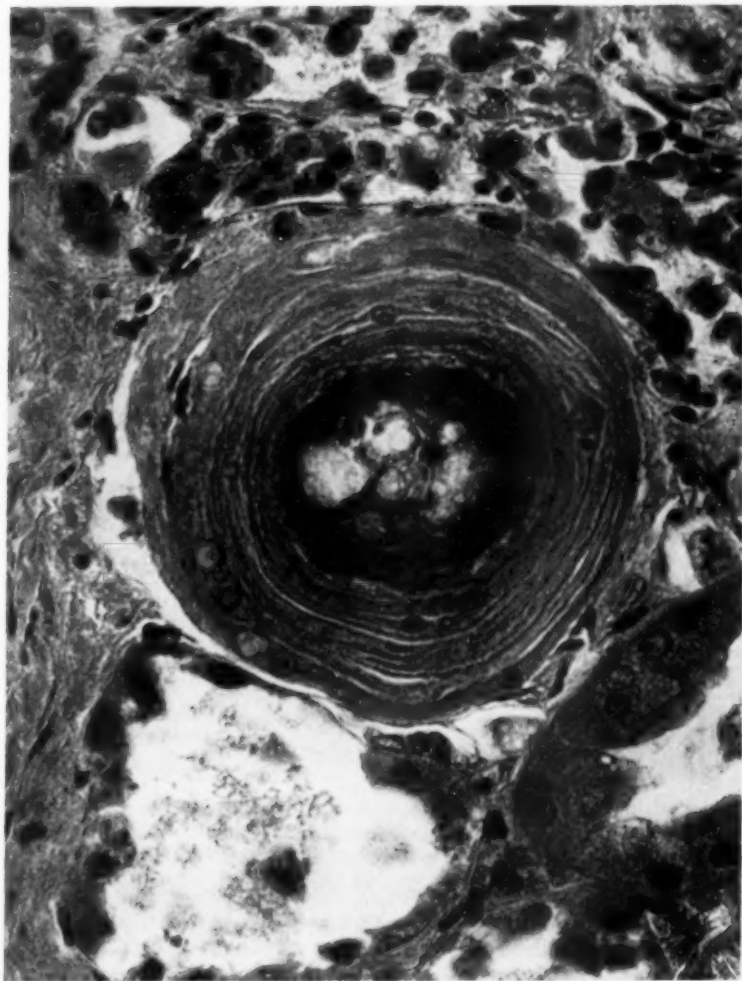


FIG. 5. Case 2. Arteriole of right kidney, demonstrating necrosis and hyperplastic changes. (Phloxine-methylene blue, $\times 800$.)

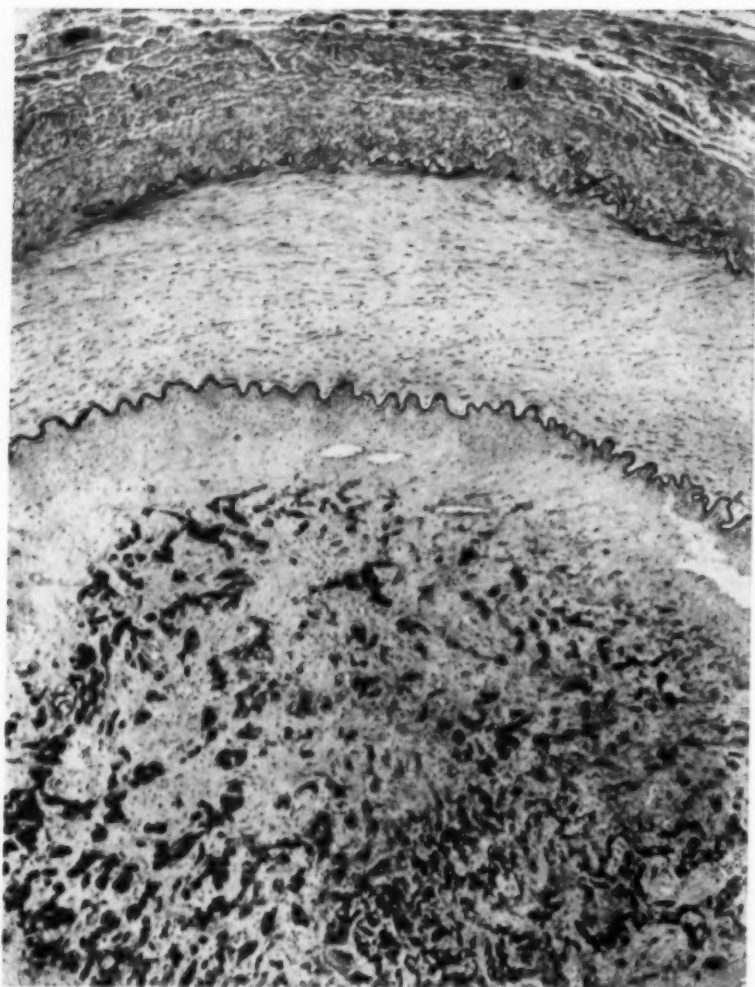


FIG. 6. Case 2. Photomicrograph of segment of thrombosed left renal artery. (Phloxine-methylene blue, $\times 80$.)

Summary: With a blood pressure of 220/150 mm. of Hg, this 59 year old man was clinically considered to have essential hypertension. Pulmonary edema and bronchopneumonia developed terminally. At necropsy there was found almost complete thrombotic occlusion of the left renal artery originating at the site of and superimposed upon an atheromatous plaque. The left kidney was spared the extensive arteriolar changes encountered in

the right kidney. The latter showed hyaline arteriolosclerosis with a necrotizing lesion, as well as necrotizing glomerulitis. The left or "protected" kidney exhibited a picture of hydronephrotic atrophy, and the arteriolar lesions present were those of benign nephrosclerosis only.

Case 3. Clinical History: On September 20, 1950, a 32 year old Filipino PFC, U. S. Army, sustained a penetrating shrapnel wound of the left hemithorax while serving in Korea. The resulting hemothorax was managed by repeated thoracenteses but, despite this, marked pleural thickening had become apparent by November 15. On November 28, therefore, decortication of the left lung was performed at Tokyo Army Hospital. During this period of surgical hospitalization four urine specimens were examined, of which three disclosed 1 plus albumin and two revealed 40 to 50 red blood cells per high power field. Postoperative blood pressure determinations ranged from 90/65 to 180/130 mm. of Hg. On January 11, 1951, the patient was transferred to a convalescent center. Upon arrival he appeared disturbed, agitated and tremulous, and complained of severe headache. Blood pressure on January 15 was 190/110 mm. of Hg. Slight nuchal rigidity was noted, and the patient continued to complain bitterly of headache. Except for hyperactive reflexes, neurologic examination was unremarkable. Diagnostic lumbar puncture was within normal limits. Urinalysis showed 4 plus albumin but the sediment was not unusual. A diagnosis of hypertensive encephalopathy was made, and the patient was transferred to the 361st Station Hospital on January 15.

On admission the patient was semi-comatose and extremely hyperactive. Physical examination disclosed a moderately well developed Filipino who was poorly responsive to stimuli. The blood pressure was 224/154 mm. of Hg, and the pulse was regular at a rate of 130/minute. The eyes were slightly divergent but the fundi were unremarkable, presenting neither hemorrhage nor exudate. All passive movements of the head and neck were resisted, the neck being moderately rigid. The thorax was symmetrical and showed a well healed left thoracotomy incision. The heart was not clinically enlarged. Breath sounds at the right pulmonary base were slightly decreased, and many rhonchi were heard throughout both lung fields. The abdomen was not unusual. All deep tendon reflexes were hyperactive and equal. A Babinski sign was elicited bilaterally. There was no apparent muscular weakness. Admission leukocyte count was 29,850, with 94 per cent neutrophils. The urine had a specific gravity of 1.018 and 3 plus albumin; innumerable red and white blood cells and occasional coarse granular casts were observed in the sediment. The non-protein nitrogen was 49 mg. per cent, CO₂ combining power 57 vol. per cent, and blood total protein 7.5 gm. per cent, with an A/G ratio of 4:1. Lumbar puncture yielded clear cerebrospinal fluid, with two white blood cells (both lymphocytes) per cubic millimeter. Spinal fluid protein was 134 mg. per cent, and chlorides were 618 mg. per cent. An electrocardiogram disclosed sinus tachycardia. On January 16 the patient remained semicomatose. The blood pressure was 160/140 mm. of Hg. An electroencephalogram was interpreted as abnormal, showing evidence of diffuse brain damage compatible with encephalopathy of any etiology. There were bilateral epileptogenic foci. A decrease in amplitude on the left side was thought to represent a possible vascular lesion. Albuminuria persisted and the urinary sediment contained numerous red blood cells and occasional granular casts. The non-protein nitrogen was 81 mg. per cent. The state of the sensorium showed little change on January 17, and the blood pressure continued elevated. However, the non-protein nitrogen declined to 69 mg. per cent. Penicillin therapy was started. On January 18 the patient appeared improved. He was still confused but was sufficiently oriented to complain of headache. Therapy with ACTH (25 mg. every six hours) was begun. An electroencephalogram on January 19 showed progression of the previously de-

scribed changes. Nevertheless, continued symptomatic improvement was noted, although headache persisted. A chest x-ray was unremarkable except for thickening of the pleura on the left and evidence of partial resection of the sixth and seventh ribs on this side. The clinical and subjective status gradually became better, and on January 22 ACTH therapy was discontinued. Albuminuria was still present, however, and the sediment contained casts and red blood cells.

On January 23 a sudden deterioration in the patient's condition occurred. He became more lethargic, complained of severe frontal and suboccipital headache, and vomited twice. The blood pressure rose precipitously to 250/150 mm. of Hg. A fresh hemorrhage was noted in the left fundus oculi. The patient developed a right supranuclear facial paralysis and equivocal weakness of the right arm. Deep tendon reflexes were equal and hyperactive. Lumbar puncture disclosed an initial spinal fluid pressure of 340 mm. H₂O, which declined to 140 mm. H₂O on relaxation. Considerable relief of headache followed the lumbar puncture. However, the patient lapsed into progressively deepening coma, had a convulsive seizure, and died at 7:40 p.m. on January 23, 1951. The final clinical diagnosis was malignant hypertensive vascular disease with encephalopathy.

Pathology: Autopsy (Dr. John M. Lukeman), performed 13 hours post mortem, disclosed mild organizing bronchopneumonia of the right lung and focal interstitial pneumonitis of the left lung. Pleural symphysis existed on the left. The heart was moderately enlarged, weighing 410 gm.; the hypertrophy was predominantly left ventricular. The liver was somewhat congested. Examination of the brain showed flattening of the gyri and obliteration of many of the sulci but otherwise presented no remarkable change. The most significant findings were renal and these will be described in detail.

The right kidney was much reduced in size, weighing 40 gm. and measuring 5 by 3 by 2.5 cm. The capsule stripped with ease, revealing a relatively smooth, reddish brown surface. On section the cortex was diminished in width throughout, measuring 2 to 3 mm. The entire midportion of the kidney showed an irregular yellowish area, suggesting infarction. The calyces and renal pelvis were free of infection and presented no abnormality. The lumen of the right ureter was patent throughout but showed slight narrowing. The left kidney was enlarged, weighing 210 gm. and measuring 11.5 by 6 by 4.75 cm. The capsule stripped readily from a reddish, irregular, moderately granular surface. A small cortical cyst was present at the lower pole. On section there was seen to be good corticomedullary differentiation, the width of the cortex being 1 cm. Vascular striations were prominent throughout the cut surface. The calyces and pelvis were not unusual. The ureter was markedly dilated but not otherwise remarkable. The ostium of the right renal artery was normally patent, but 1.25 cm. from its aortic origin the lumen was almost completely occluded by a firm, inelastic mass consistent with a fragment of corroded metal. The portion of the artery distal to this was narrowed and atrophic (figure 7). The left renal artery was widely patent and showed no atheromatous change. The lumen appeared enlarged, measuring 0.8 cm. in diameter.

Microscopic examination of sections of the ischemic right kidney disclosed an obliterative endarteritis of medium and small arteries in the area of grossly evident infarction, as well as extensive cicatricial change. Sections from the cortex in this region exhibited focal accumulations of chronic inflammatory cells, chiefly lymphocytes. Many tubules in the area presented degeneration, dilatation and fibrosis, and occasional glomeruli were fibrotic and hyalinized. Elsewhere the general architecture of the kidney was not unusual, and arteriolar changes in areas not encompassed by the infarct were absent.

On the left, microscopic alterations of the glomeruli and tubules were less pronounced than in the area of infarction. However, fibrotic glomeruli were scattered

throughout. Small foci of inflammatory cells were seen in the cortex. Marked proliferative arteriolar lesions were noted but were not extensive in distribution. Necrotizing arteriolitis was occasionally seen.

Microscopic examination of sections of the right renal artery at the point of entrance of the metallic foreign body showed fragmentation and degeneration of the smooth muscle of the arterial wall. In addition to the microscopic findings already



FIG. 7. Case 3. The right (ischemic) kidney, viewed from behind, with attached renal artery and ureter. The arrow indicates the metallic foreign body within the opened renal artery. The infarcted area is seen in the midportion of the kidney.

described, slight arteriolar proliferation was observed in sections of the heart and spleen. Spectrographic analysis of the mass found in the lumen of the right renal artery indicated it to have the composition of steel.

The final pathologic diagnosis was malignant nephrosclerosis of the left kidney secondary to obstruction of the right renal artery by a metallic foreign body.

Summary: This 32 year old infantryman with no known previous history of hypertension sustained a penetrating wound of the left hemithorax from shrapnel. Two months after injury, decortication of the left lung was performed. At this time albuminuria and hematuria were noted. These findings persisted. A rapidly and inexorably progressive hypertension developed and was associated with severe encephalopathy. The patient became



FIG. 8. Case 3. Photomicrograph of right kidney, demonstrating well circumscribed infarct on left. (Hematoxylin and eosin, $\times 32$.)

comatose and died in a convulsive seizure four months after being wounded. Autopsy disclosed that the lumen of the right renal artery had been almost completely occluded by a metallic foreign body which had lodged at that site after traversing the left hemithorax. The resulting ischemic kidney showed marked atrophy and partial infarction, but was free of the arteriolar changes of malignant nephrosclerosis. The intact contralateral kidney, however, exhibited compensatory hypertrophy and the microscopic lesions of malignant nephrosclerosis.

DISCUSSION

The association of unilateral renal disease and severe persistent hypertension was emphasized by the clinical observations of Ask-Upmark⁵ in 1929. However, experimental confirmation awaited the work of Goldblatt.^{1,2,3} His initial studies were carried out in the dog and indicated that a sustained hypertension could be effected either by partial bilateral renal artery constriction or by complete unilateral constriction with contralateral nephrectomy, and that the elevation of blood pressure was merely transient if unilateral renal artery constriction coexisted with an intact contralateral kidney. Nevertheless, in experiments conducted on other species these conditions have not been found necessary and it has been possible to produce a permanent hypertension by unilateral obstruction only.^{6,7} In addition, evidence has accumulated which confirms earlier observations and indicates that, in man also, unilateral renal ischemia alone may be sufficient to induce a persistent hypertension. The difficulties and pitfalls of attempting to interpret clinical cases in the light of experimental data have been well summarized by Yuile,⁸ who critically surveyed the problem of the relationship between obstructive lesions of the main renal artery and hypertension in man. This author concludes that although "there has perhaps been too great a tendency to assume the action of a 'Goldblatt mechanism' merely because of the presence of a lesion which narrowed the lumen of one or both main renal arteries, . . . it is noteworthy that no evidence, opposed to the view that experimentally produced hypertension has a human counterpart, was encountered."

There have been several clinical reports of unilateral renal artery occlusion associated with hypertension and cured by nephrectomy, but probably the most significant and convincing instance of a Goldblatt phenomenon occurring clinically is the case recorded by Leadbetter and Burkland.⁹ The patient was a five year old boy with severe hypertension who experienced permanent reversion¹⁰ to the normotensive state following surgical removal of the right kidney, the renal artery to which was found to be almost completely occluded by a mass of smooth muscle.

According to the mechanism of obstruction, Yuile⁸ properly classifies obstructing renal artery lesions as extrinsic or intrinsic. Included as examples of extrinsic etiology are those due to external compression of the renal artery by such varying pathologic entities as lymphosarcoma,¹¹ hydatid

cyst,¹² aortic aneurysm¹³ and organized hematoma.¹⁴ Additional extrinsic causes of renal artery constriction are the kinking and torsion associated with nephroptosis^{15, 16} and aneurysm of the renal artery.^{17, 18, 19, 20} As an example of an intrinsic lesion, mention has already been made of the case reported by Leadbetter and Burkland,⁹ in which the lumen of a renal artery was occluded by a smooth muscle tumor, presumably congenital in origin. Price and Skelton²¹ have presented a case of bilateral renal artery constriction due to syphilitic arteritis in a young woman, with death from hypertensive heart disease occurring at the age of 24. The pathologic picture was complicated by the concomitant finding of atheromata in the renal arteries, but the authors considered this to be a secondary lesion. Apart from these and similar unusual causes, however, instances of intrinsic etiology are limited to those due to arteriosclerotic plaques and those due to thrombosis. The latter may be embrogenic or may develop in situ.

The possible relationship between arteriosclerotic narrowing of the renal artery and hypertension has been investigated by several workers, with inconclusive results. On the basis of 50 autopsies, Blackman²² suggested a direct correlation between the presence of arteriosclerotic plaques in the renal arteries and a clinical history of hypertension. Richardson,²³ in a similar study, also proposed such a correlation. However, Yuile⁸ believes that the method of postfixation measurement employed by these authors undoubtedly exaggerated the degree of stenosis actually present. Oppenheimer, Klemperer, and Moschkowitz⁴ analyzed the clinical and postmortem findings in 18 instances of unilateral arteriosclerotic renal artery constriction and concluded that the narrowing was an effect rather than a cause of the elevated blood pressure. In an additional pathologic study, Lisa and co-workers²⁴ were unable to establish even a superficial relationship between renal artery sclerosis and a history of hypertension. In the light of current knowledge, the problem is unresolved.

In contrast to arteriosclerotic constriction, instances of unilateral renal artery thrombosis furnish more acceptable data relative to Goldblatt-type hypertension occurring in man. Clinically and pathologically, the distinction between renal artery thrombosis secondary to embolus and that developing in situ is difficult to establish and frequently is based on inferential data only. However, the precise nature of the initiating factor does not appear to alter the subsequent pathologic process.

The clinical importance of thrombotic renal artery lesions was suggested by Boyd and Lewis,²⁵ who noted relief from hypertension following surgical removal of a partially infarcted kidney. Nevertheless, Yuile⁸ expresses doubt regarding the validity of considering this case as one of Goldblatt hypertension because of the presence of widespread renal vascular lesions which were thought to be of greater significance than the infarct. Fishberg²⁶ has presented four cases of hypertension associated with embolism of the renal artery, and a case of embrogenic thrombotic occlusion of both

renal arteries with hypertension has been reported by Prinzmetal et al.²⁷ An instance of malignant hypertension secondary to embolic occlusion of the right main renal artery in a 43 year old man has recently been described by Blahd et al.²⁸ Saphir and Ballinger²⁹ recorded the case of a 46 year old man who developed severe hypertension and who was found at autopsy to have thrombosis of the left renal artery and malignant nephrosclerosis of the right kidney. Yuile⁸ incorporated in his excellent review two additional cases of unilateral renal artery thrombosis associated with hypertension, one patient dying after surgical removal of the defective kidney and the other before contemplated nephrectomy could be performed. A clinical parallel to the initial experimental work of Goldblatt^{1,2,3} in dogs has been reported by Bumpus.³⁰ The patient was a 27 year old man with unexplained hypertension. Intravenous pyelography showed nonfunctioning of the left kidney. A left nephrectomy was performed, during the course of which the blood pressure dropped from the preoperative level of 220 mm. Hg to 130 mm. Hg. Pathologic examination of the surgical specimen disclosed a markedly contracted kidney. The patient was normotensive following nephrectomy, but on the eighth postoperative day an episode of dyspnea and cyanosis occurred and the blood pressure suddenly rose to 250/150 mm. of Hg. Exitus followed on the fourteenth postoperative day, and autopsy showed a recent thrombus in the right renal artery. Goodman³¹ has recorded the case of a 22 year old woman with malignant hypertension initiated by thrombotic occlusion of the right renal artery, death occurring as the result of progressive hypertension.

Emphasis on the clinical aspects of renal artery thrombosis³² has been followed by an increase in the number of instances diagnosed ante mortem. Goodyear and Beard³³ reported the case of a 62 year old woman with acute total thrombotic occlusion of the right renal artery. Diagnosis was suggested by the clinical history and confirmed by a series of complete pyelographic studies which indicated nonfunction and progressive atrophy of the right kidney, with compensatory hypertrophy of the contralateral kidney. Corroboratory evidence was obtained by arterial catheterization studies. Long standing arteriosclerosis and hypertension had been present prior to the renal artery thrombosis, and the latter had been followed by no significant alteration in the level of the blood pressure. The patient showed moderate temporary improvement on medical management but died in coma nine weeks after the acute episode. Autopsy confirmed the presence of total thrombotic occlusion of the right renal artery. In the case of Shea et al.,³⁴ a 33 year old man with hypertension experienced permanent reversion to normotension after removal of the left kidney, the main artery to which was obstructed by a thrombus. Cornwell³⁵ described a 35 year old woman in whom the sudden development of renal artery occlusion, presumably thrombotic, was associated with severe hypertension. Nephrectomy restored the normotensive state and the patient became symptom-free.

The cases herein described are presented as probable clinical counterparts of Goldblatt's experimental hypertension. The validity of Yuile's⁸ caution against considering any occlusive renal artery lesion with associated hyperpiesis as an example of the Goldblatt mechanism is well appreciated, and certainly in these cases the evidence is not incontrovertible. Nevertheless, it is felt that the occurrence of renal artery thrombosis was the most important single factor in the pathogenesis of the severe hypertension in cases 1 and 2. In case 3 the previous history and the temporal relationships are such that the obstruction of the renal artery by the metallic foreign body may almost certainly be accorded a direct etiologic rôle in the production of malignant hypertension.

In the first case the initial hospitalization at the age of 44 appears to have been prompted by the clinically undiagnosed renal artery thrombosis. Hematuria persisted for seven months and then disappeared. The blood pressure, however, remained elevated, and the patient died four years later of massive pontine hemorrhage which was undoubtedly related to the severe hypertension. A roentgenogram of the abdomen secured for other purposes shortly before death delineated an apparently normal kidney on the left, while that on the right was obscured. Although the significance of such a finding is often difficult to assess, perhaps it should have suggested further investigation of the functional capacity of the kidneys. Autopsy showed almost complete occlusion of the right renal artery by an old thrombus. On microscopic examination the right kidney presented changes consistent with benign nephrosclerosis, while the left kidney exhibited the picture of malignant nephrosclerosis in addition. As has been suggested by others,⁹ renal artery obstruction appears to exert a "protective" action on the ischemic kidney, while the kidney with unimpaired vascular supply bears the full brunt of the hypertension and may exhibit the changes of malignant nephrosclerosis. This also concurs with the generally accepted view that the histologic alterations seen in the kidneys of patients with malignant hypertension are the result rather than the cause of the elevated blood pressure.

The second case was that of a 59 year old man clinically considered to have essential hypertension. Although the patient was in an age group in which hypertension is not uncommon, rapid progression of cardiovascular symptomatology during the three year period prior to death may well have been related to the renal artery thrombosis. Unfortunately, there were no data available relative to the level of the blood pressure prior to the final hospitalization. Death occurred in pulmonary edema, and necropsy disclosed an old thrombus of the left renal artery. The microscopic findings were similar to those in case 1, with the lesions of malignant nephrosclerosis restricted to the kidney with intact blood supply.

Case 3 represents a unique mechanism of renal artery obstruction. Fulminating hypertension developed in a 32 year old soldier following a thoraco-abdominal wound, and terminated fatally four months later. The absence of a previous history of hyperpiesis incriminates the unilateral renal ischemia

even more strongly as the essential factor in its pathogenesis. Histologically, the nonischemic kidney presented the lesions of malignant nephrosclerosis, while the contralateral kidney, apart from the site of the infarct, showed no arteriolar pathology. X-ray studies of the abdomen might have revealed the presence and position of the metallic fragment and thereby suggested the diagnosis, but unfortunately they did not appear indicated.

In neither of the first two cases was the diagnosis of renal artery thrombosis considered clinically. This would suggest that more attention should be accorded the possibility of renal artery thrombosis in older patients with newly developed or recently accentuated hypertension, especially in view of the fact that intravascular clotting is more common in this age group. In the third case as well, the diagnosis of renal artery occlusion was not considered. The possible diagnostic advantages of complete pyelographic and other urologic studies in such instances of fulminating hypertension are thereby indicated. Since hypertension of this etiology is one of the unfortunately few types for which curative means are available, recognition assumes added importance.

The results of urinalysis in instances of renal artery occlusion are inconstant and appear to depend in great measure upon the duration and degree of the obstruction, as well as the presence or absence of additional renal lesions. Hematuria and albuminuria are almost always present initially. After a variable period, erythrocytes disappear from the sediment but albuminuria usually persists. In case 1, hematuria subsided after seven months but albuminuria continued until death. In the second case only one urine examination was done before death, and this revealed four to six red blood cells per high power field but no albumin. Albuminuria and hematuria were consistently present in case 3. The ability to concentrate urine may be impaired or the specific gravity may show no abnormality. This would appear to depend directly upon the physiologic reserve of the kidney with intact blood supply.

Microscopic examination of the nonischemic kidney in all three cases showed necrotizing arteriolar lesions. However, these are not essential elements in the pathologic picture of malignant nephrosclerosis, and the work of Kimmelstiel and Wilson³⁶ has indicated that the occurrence of marked hyperplastic arteriolar sclerosis is adequate basis for this diagnosis. Necrotizing arteriolitis merely mirrors the presence of renal insufficiency.

While unilateral renal artery obstruction may obviously be effective in the production of severe hypertension, it would appear that the renal ischemia resulting therefrom must be relative and not absolute. In all three cases herein described the obstruction was "almost complete" but definitely not total. Cornwell³⁵ has stated that "arterial hypertension can result from any type of renal disease that produces a marked reduction, but not complete ablation of the blood flow through the kidney." In a noninfected kidney, complete renal artery occlusion results in total aseptic infarction and

autonephrectomy³⁷ without increment in blood pressure. This would explain the absence of any alteration of the blood pressure in such cases as that of Goodyear and Beard,³⁸ in which the renal artery obstruction was complete.

Since diagnostic accuracy is a prerequisite to intelligent management, brief review of the available means of achieving this end may be helpful. It may appear platitudinous, but it is nevertheless true that the first essential in establishing such a diagnosis is a consideration of its possibility. In discussing the manifestations of acute renal artery thrombosis, Goodyear and Beard³⁸ indicate that such factors as pain, leukocytosis and alterations in the urine may be variable, and state that the most important single diagnostic element is a complete urologic examination, which should include cystoscopy, ureteral catheterization and pyelographic studies. Renewed interest in the technic of aortography has afforded a definitive diagnostic tool for the study of this lesion. In general, the trend has been toward simplification. Goodwin et al.³⁹ compared the results of the translumbar needle puncture method with those obtained by percutaneous retrograde catheterization of the aorta, and suggested that the former is the procedure of choice, with the latter reserved for the few instances in which the simpler approach is unsatisfactory. Excellent results have also been obtained by Peirce,³⁹ who advocates percutaneous femoral artery catheterization. But perhaps the most impressive series is that of Smith et al.⁴⁰ These workers have utilized the technic of translumbar needle puncture of the aorta in over 1,000 cases without a fatality or even a significant complication. On two occasions renal artery obstruction was demonstrated by this method, illustrating its value in the diagnosis of such lesions.

SUMMARY AND CONCLUSIONS

Three instances of unilateral renal artery obstruction associated with malignant hypertension have been presented. These are considered to constitute a clinical parallel to the experimental Goldblatt phenomenon. Renal artery thrombosis should not be overlooked as an etiologic factor in older patients with newly developed or recently accentuated hypertension. With the technical refinement of aortography, safe and reliable methods are available for the study of this lesion. Since hypertension of this etiology has been shown to be amenable to surgery, early diagnosis is important.

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NECROTIZING RENAL PAPILLITIS *

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INTRODUCTION

THIS paper includes a review of the literature regarding necrotizing renal papillitis and a report of three interesting cases. Our principal purpose in presenting this subject is to emphasize its possible existence as a specific entity, and also to stimulate an interest in and create an awareness of its presence. It has been our experience that many physicians are either not cognizant of the disease or at least do not differentiate it from acute pyelonephritis. The diagnosis is frequently overlooked because of one of two factors: a lack of general knowledge of and familiarity with the condition, or a failure to consider its potential existence when dealing with acute renal insufficiency.

HISTORY AND INCIDENCE

Necrotizing renal papillitis is a severe, usually fatal type of suppurative renal infection. It most frequently occurs in diabetic patients but is also seen in nondiabetics. A review of the recent literature reveals that this disease has received little mention, especially in the United States. Friedreich¹ first described the anatomic lesion in 1877. He reported a case of a 70 year old man with prostatic disease, hydronephrosis and bilateral papillary necrosis. It was his opinion that necrosis of the papillae was due to urinary stasis with pressure atrophy and also a decrease in blood supply to the local areas.

Turner² reported three cases from 1885 to 1888, including a woman who had associated diabetes mellitus. Stoudensky³ reported six cases in 1899, all associated with obstruction of the urinary tract. Four of his patients had calculi, two benign prostatic hypertrophy. Schömer⁴ reported three cases in 1931, one a diabetic and two nondiabetic. Grauhan⁵ in 1934 reported two cases, both occurring in nondiabetics. Both of these patients had unilateral necrotizing renal papillitis secondary to an obstructing calculus.

In 1937, Gunther⁶ first emphasized the association of this disease with diabetes mellitus. He had observed the lesions in 10 instances, seven of which occurred in individuals with ascending suppurative pyelonephritis. In eight of his cases there was associated diabetes mellitus. In the same year Sheehan⁷ reported a case in an 18 year old nondiabetic primipara who developed renal failure post-partum. He believed the necrotizing process obstructed the collecting tubules, thus largely destroying renal function.

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In 1938, Alken⁸ reported four cases of papillary necrosis associated with diabetes mellitus. In three of his cases the disease was unilateral and a nephrectomy was performed. He emphasized the importance of the following triad: diabetes mellitus, decrease in renal function and characteristic pyelographic findings. He believed nephrectomy to be indicated only in those patients with unilateral disease who demonstrate a loss of renal function on the involved side.

Mellgren and Redell⁹ in 1941 reported this disease in two nondiabetic patients. One case was interesting in that, following a nephrectomy on one side, the patient died several weeks later with a similar condition appearing in the remaining kidney. The second case was an elderly man with benign prostatic hypertrophy, urinary retention and uremia. Harrison and Bailey¹⁰ in 1942 reported three cases of necrotizing pyelonephritis in diabetic individuals. The first patient demonstrated a well advanced urinary infection many months before its recognition and treatment. The second patient had mild diabetes and a urinary infection which had been present for several years. The third patient had fulminating pyelonephritis due to *Escherichia coli*, and this infection had probably been present long before the onset of the terminal illness.

In 1944, Davson and Langley¹¹ reported a case in a 28 year old woman originally diagnosed as having chronic nephritis. The pathologic findings in their case strongly suggested that it began as a diffuse pyelonephritis and terminated with necrotizing papillitis. In 1945 Eskelund¹² reported an interesting case in which papillary necrosis followed retrograde pyelography. This author was convinced that the terminal renal lesions were the result of the dye utilized (25 per cent solution of sodium orthoiodohippurate) in the pyelography. In 1946 Robbins, Mallory and Kinney¹³ presented a review of 26 autopsied cases of necrotizing renal papillitis, 19 of which occurred in diabetic subjects. The authors divided their cases, clinically, into fulminating and subacute types. The former were characterized by a sudden onset of severe infection; the latter had pyelonephritis for long periods, which finally became severe and terminated in the fulminating type.

In 1947 Edmondson, Martin and Evans¹⁴ reported on 29 cases of necrotizing renal papillitis occurring in an analysis of 859 diabetic subjects among a series of 32,000 autopsies. They also reported 21 cases, among 1,023 patients with pyelonephritis, who were not diabetic; in 20 of these latter cases the disease occurred as a complication of urinary obstruction.

The etiology and pathogenesis of this disease are as yet not completely determined. Certain basic facts which are known, however, merit both discussion and further consideration. Infection, either locally in the urinary tract or systemically, obviously plays a major rôle in the pathogenesis of this condition. The facility with which infections develop in diabetic patients suggests that various bacteria in the urinary tract are a potential hazard and must be more seriously considered than in the nondiabetic individual. The

presence of pyuria indicates that infection has already developed and, in all probability, that destruction of the tissue has ensued. It has long been established that, in the absence of diabetes, necrotizing renal papillitis is usually secondary to obstruction in the urinary tract. This latter fact also serves to emphasize the rôle of infection resulting from obstruction in the nondiabetic patient.

Baldwin and Root¹⁵ have demonstrated that approximately 20 per cent of people dying of diabetes mellitus have infection of the kidneys. Urinary infection is found at autopsy five times as frequently in patients with diabetes as in the population at large. Robbins and Tucker¹⁶ analyzed 307 autopsied diabetic cases as compared to 2,800 autopsied nondiabetic subjects. They found acute pyelonephritis to be four and one-half times as frequent a cause of death in the diabetic group as in the control group, and, moreover, to rank sixth among the causes of death in the former group. In 64 of their cases with parenchymal renal involvement 16 (25 per cent) were hematogenous infections; one was unclassified. They found the mortality rate to be very high in diabetics with hematogenous infections, owing to the fact that hemolytic *Staphylococcus aureus* was usually the causative organism. Colon bacillus was found to be the most frequent offender in ascending urinary infections. Sharkey and Root¹⁷ found 35 cases (18 per cent) of purulent renal infections in 196 autopsied diabetic individuals.

Harrison and Bailey¹⁰ postulate that the fulminating form of "necrotizing pyelonephritis" may well arise from mild, asymptomatic and frequently neglected instances of urinary infection in patients who have diabetes. These same authors, in an attempt to determine the incidence of asymptomatic bacteriuria and pyuria in ambulatory patients, compared a group of 50 unselected diabetic patients with another group of patients of similar age distribution in whom diabetes was not present. Numerous bacteria were found in the urine six or seven times as frequently when diabetes was present as when it was absent. Pyuria was found five times as often among the diabetics as among the controls. These authors also presented three cases of diabetes, with urinary infections of varying durations, who eventually developed "necrotizing pyelonephritis."

Davson and Langley¹¹ postulated three possible etiologic factors for this disease: vascular, mechanical and toxic. They admit there is little evidence to support vascular occlusion or mechanical pressure on the blood vessels of the pelvis as causative agents. They do feel, however, that constituents of diabetic urine and products of bacterial metabolism may exert a direct toxic action on the renal papillae. Mallory, Crane and Edwards¹⁸ viewed involvement of the renal pyramids as one of the early lesions of experimental pyelonephritis. These authors experimentally produced necrosis of the renal papillae in nondiabetic rabbits by ligating one ureter and injecting organisms intravenously. No lesions developed in the nonobstructed kidney.

Edmondson et al.¹⁴ list three factors worthy of consideration as etiologic

agents in the necrotizing lesions. First, the papillae and the pyramids have a poor blood supply as compared with the rest of the kidney. Almost all of the blood reaches the peritubular capillaries after it has gone through the glomeruli. This blood has lost 10 per cent of its water and much of its sugar, chlorides and nitrogenous products, while retaining its protein, thus increasing its osmotic pressure. Being more viscid, it tends to undergo intravascular clotting more readily. Sclerotic changes in the arterial tree further impair the circulation. Second, the presence of diabetes plays an important rôle. In diabetic acidosis, the ketone bodies cause a rapid disappearance of polymorphonuclear leukocytes and the mononuclear cells predominate. Thus, when the basement membranes become necrotic, one must consider the effects on the intercellular tissues of a urine rich in bacteria, highly acid and concentrated with sugar. In the presence of such conditions, the tissues may be unable to cope with the infection. In obstruction of the urinary tract, urine may escape into the tissues through the necrotic walls. Third, the type and virulence of the bacteria must be strongly considered. *S. aureus* and *E. coli* are the organisms most frequently involved in this process. Diabetic patients demonstrate very poor resistance to *S. aureus*, as evidenced by their susceptibility to carbuncles and cellulitis.

PATHOLOGY

The gross lesions are rather typical in appearance. The gray-yellow or yellow-green necrotic papillae stand out in distinct contrast to the remainder of the renal tissue. Depending upon the stage of the lesion, the greater portion of a pyramid or merely the tips of the papillae may be necrotic. In very advanced lesions, sequestration of the papillae may occur and the tissue may slough into the lumen of the kidney pelvis. The lesions rarely extend more peripherally than one-half to two-thirds the distance from the tips of the papillae to the pyramidocortical junction. The condition is usually bilateral but may involve only one kidney, especially when it occurs secondary to ureteral obstruction. One may encounter associated acute pyelonephritis in the cortex of the involved kidneys.

Microscopically, there are small to large areas of coagulation necrosis involving one or more of the renal papillae. There is frequently a complete loss of normal renal architecture. Surrounding the area of infarction there is a zone of dense inflammatory exudate, and many of the tubules are filled with similar material. Peripheral to this is a zone of hyperemia and edema. All of our microscopic specimens demonstrated a very intense infiltration with polymorphonuclear leukocytes in both the interstitial tissue and the tubules. This latter finding is in contrast to that of many other authors, who report a paucity of polymorphonuclear cells and a predominance of mononuclear cells, especially in diabetic subjects. As mentioned previously, several investigators are of the opinion that the polymorphonuclear leukocytes are destroyed or disintegrate in the presence of the ketone bodies which

occur in diabetic acidosis. We were impressed with the minimal amount of vascular alteration in both the arterioles and glomeruli. As was previously stated, in reviewing the literature, a number of authors were impressed with the vascular changes in the kidneys, and some even postulate vascular lesions as a probable etiologic factor in this disease. Even our diabetic patient failed to demonstrate any evidence of Kimmelstiel-Wilson lesions.

CASE REPORTS

Case 1. A 55 year old white female was admitted to the medical service of St. Francis Hospital on January 18, 1950. She complained of weakness and anorexia for approximately three weeks. Several months prior to admission she had noted swelling of the legs, which responded to salt restriction in her diet; the edema was intermittently present following its onset. A week prior to admission she developed a nonproductive "brassy cough," "choking spells" and five to six watery stools per day. Four days prior to admission she developed oliguria, gross hematuria and burning on urination. She emphatically denied any symptoms of a similar nature prior to the present illness. The anorexia was accompanied by a weight loss of five to six pounds. There were no chills, fever or costovertebral or suprapubic pain. She had had an appendectomy and pelvic laparotomy 20 years previously. In 1948 she had had surgical treatment for a "ruptured stomach." She denied the use of tobacco, alcohol and drugs. The family history and review of systems were noncontributory.

Physical examination revealed an acutely ill, thin, sallow white female. She was somnolent and very difficult to interrogate or examine. Her temperature was 98.6° F.; pulse, 80; respirations, 20; blood pressure, 130/70 mm. of Hg. The pupils were constricted and there was a mucopurulent conjunctivitis; the fundusoscopic examination was essentially within normal limits. The tongue was red and smooth. There were several spider nevi on the chest and over both shoulders. There was no evidence of thyroid enlargement, lymphadenopathy or venous engorgement in the neck region. The cardiac findings were normal and the lungs were clear. Examination of the abdomen revealed the liver to be palpable 8 cm. below the right costal margin; it was hard in consistency, the edge rounded and the surface smooth. The spleen was not palpable. There was no evidence of costovertebral angle tenderness and the kidneys were not palpable. The pelvic examination was not remarkable. The neurologic findings were normal and the extremities revealed evidence of emaciation. The impression on admission was portal cirrhosis and possible miliary tuberculosis.

The blood count on admission revealed 3,000,000 red cells, 10.7 gm. of hemoglobin and 36,350 white cells, with 96 per cent polymorphonuclear leukocytes. The urine was cloudy, acid in reaction, contained 150 mg. of albumin and was negative for sugar; on microscopic examination there were many white blood cells in clumps, 10 to 15 red cells and numerous gram-negative bacilli. The admission blood urea nitrogen was 150 mg. per cent, fasting blood sugar 106 mg. per cent, and the total serum proteins were 4.5 gm. per cent, with a normal albumin-globulin ratio. The sedimentation rate (Westergren) was 135 mm. per one hour. The blood Kahn test was negative. The cephalin flocculation was 3 plus in 48 hours, and the carbon dioxide combining power was 31 vol. per cent. The serum phosphorus was 6.3 mg. and the spinal fluid was entirely normal. The urine culture was positive for *E. coli*. A flat plate of the abdomen revealed the kidney silhouettes to be normal in size. There was a suggestion of free fluid in the peritoneal cavity, but the plate was otherwise not remarkable.

The patient was hospitalized for six days, during which time she remained afebrile. She ate poorly and was given a daily average of 2,000 c.c. of 5 per cent glucose in distilled water intravenously. Her urinary output averaged from 150 to 300 c.c. daily and decreased to 45 c.c. on the last hospital day. She vomited coffee-ground material, and Wangensteen suction was instituted two days prior to death. Terminally she lapsed into coma and her blood urea nitrogen elevated to 212 mg. per cent. Antibiotic therapy consisted of dihydrostreptomycin, 0.5 gm. twice daily for six days, and aqueous penicillin, 50,000 units every three hours during the last hospital day.

Autopsy: The arterial embalming was performed prior to the postmortem examination. The important autopsy findings were confined to the following organs: The right and left lungs weighed 440 and 430 gm., respectively; they demonstrated acute purulent bronchitis and early focal bronchopneumonia. The right kidney weighed 200 gm., the left 175 gm., and they were similar in appearance. The cortical surfaces were smooth and showed petechial hemorrhages. Both kidneys (figure 1)



FIG. 1. Case 1. Gross section of the kidney, illustrating necrosis of the renal papillae.

were swollen, and the cut surfaces revealed blurring of the corticomedullary markings. The tips of the renal papillae revealed large yellow areas of necrosis surrounded by radiating dark red zones. The pelvic mucosa, adjacent to the tips of the papillae, was dark red in color. There was no evidence of obstruction in the ureters or the lower urinary tract.

Histologically, the kidneys (figure 2) revealed areas of coagulation necrosis involving the renal papillae, complete loss of recognizable architecture, and scattered foci of inflammatory cells, mainly mononuclear in character. In the periphery of the infarcted areas there was a zone of dense inflammatory exudate, and the tubules were filled with dark staining debris. Surrounding this was an area of hyperemia and edema. The remainder of the cortex was involved by a dense leukocytic infiltration, in the interstitial areas as well as in the tubules. The vascular tree, including the glomeruli and arterioles, was normal. A few subcapsular hemorrhages were also present. The final anatomic diagnoses were acute necrotizing renal papillitis of both kidneys and early bronchopneumonia.

Case 2. A 65 year old white female was admitted to the medical service of St. Francis Hospital on September 19, 1951. The patient was in coma, and a history obtained from two sisters revealed that she had been a known diabetic for several years but had refused to take insulin or to adhere to a diet. She was known to have had hypertension for many years. Three weeks prior to admission she developed nausea, vomiting and severe right upper quadrant abdominal pain radiating to the interscapular area. These symptoms continued intermittently until three days prior to

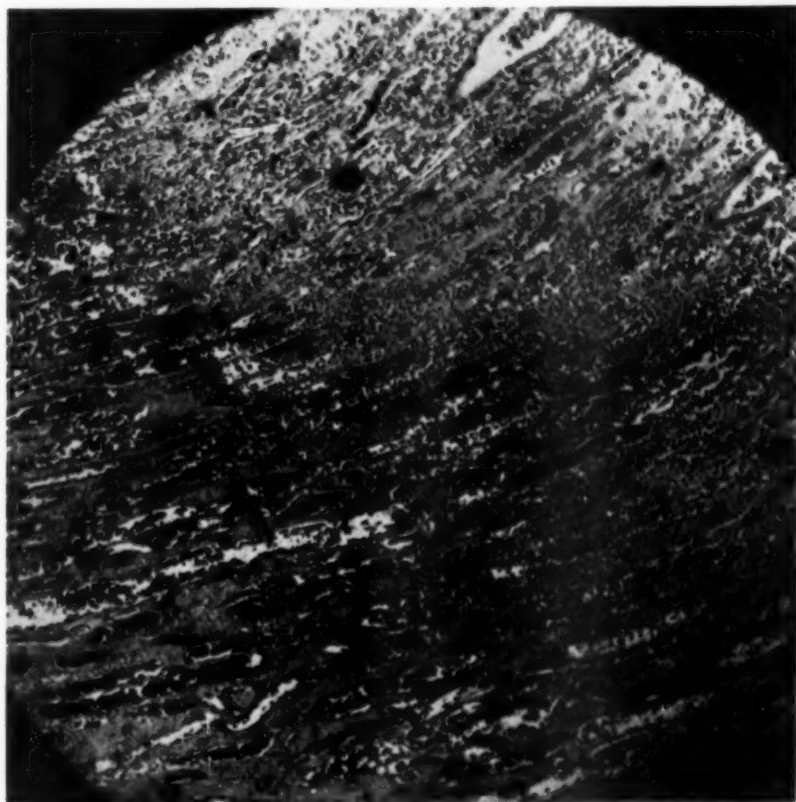


Fig. 2. *Case 1.* Photomicrograph illustrating an area of coagulation necrosis in the lower half and a zone of inflammatory exudate in the upper portion.

admission, at which time she became mentally confused and experienced difficulty in walking. The following day her left arm and left leg became paralyzed. The abdominal pain persisted and she developed a high fever. It was noted that she passed large quantities of urine. The day prior to admission an attending physician gave her an injection, following which she slept throughout the night. On the day of admission she could not be aroused, and bloody urine was found on her bed clothing.

The past history revealed rheumatic fever in adolescence without known sequelae. She had also suffered from recurrent "gall-bladder attacks." She had been treated

for varicose ulcers of the right ankle over a period of seven years, and an ovarian cyst had been removed 30 years previously. One sister had diabetes mellitus, but the family history was otherwise noncontributory. A review of systems revealed no additional facts of significance.

Physical examination revealed a well developed and well nourished elderly white female in a semicomatose state. The head and eyes were deviated toward the right and there were frequent gross tremors of the right hand, right arm and right leg. The left arm and left leg were flaccid. Her temperature was 104° F.; pulse, 160; respirations, 40; blood pressure, 180/60 mm. of Hg in both arms. There were numerous petechial hemorrhages on the arms, legs and trunk, and a clean varicose ulcer on the medial aspect of the right ankle. The eyes revealed constriction of the pupils and petechiae in the conjunctiva, and the fundoscopic examination was unsatisfactory. The ears, nose and throat were normal except for dryness and fissuring of the mucosa. The neck was moderately rigid and the right lobe of the thyroid was diffusely enlarged. The thorax was symmetrical and the lungs were clear. The heart was enlarged to the left and there was a rapid sinus rhythm; there was a high pitched blowing apical systolic murmur. The abdomen was rounded, soft and obese. The liver, which was palpable 5 cm. below the right costal margin, had a smooth surface and a sharp edge. The neurologic examination demonstrated a flaccid paralysis with increased deep tendon reflexes in the left arm and left leg. The clinical impression on admission was diabetes mellitus, acute bacterial endocarditis, cerebral embolization, septicemia and stasis ulcer of the right ankle.

The blood count on admission revealed 4,500,000 red blood cells, 13 gm. of hemoglobin and 30,000 white cells, with 95 per cent polymorphonuclear leukocytes. Thirty cubic centimeters of grossly bloody urine were obtained by catheterization; the urine had a specific gravity of 1.014 and was acid in reaction. It contained 40 mg. of albumin and no acetone, and gave a 2 plus reaction for sugar by the qualitative Benedict's test. There were clumps of white blood cells and innumerable red blood cells on microscopic examination. The admission blood urea nitrogen was 160 mg. per cent, the blood sugar 600 mg. per cent and the carbon dioxide combining power 19 vol. per cent. The serologic test for syphilis was negative and the Westergren sedimentation rate (uncorrected) was 115 mm. per one hour. The total serum proteins were 7.04 gm. per cent with a 1:1 albumin globulin ratio. The thymol turbidity was six units, serum amylase 82 units, and serum chlorides 485 mg. per cent. The spinal fluid revealed 210 red cells, 10,000 white cells per cubic millimeter, 350 mg. sugar, 632 mg. chlorides, 30 mg. protein, a normal gum mastic curve and a negative Wassermann test. Both the urine and blood cultures were positive for *Aerobacter aerogenes*. The serum alkaline phosphatase was 7 units and the cephalin flocculation was 4 plus in 24 hours.

Four hours following admission and treatment, the blood sugar was 347 mg. per cent and the carbon dioxide combining power was 28 vol. per cent. Sixteen hours after admission the blood sugar was 400 mg. per cent, the carbon dioxide combining power 28 vol. per cent, the blood urea nitrogen 140 mg. and the serum chlorides 475 mg. per cent. The electrocardiogram demonstrated a sinus tachycardia and a left heart strain pattern.

During a hospital course of 60 hours the patient ran a septic temperature which elevated terminally to 105° rectally. Her catheterized urine specimens contained 2 plus sugar and were consistently negative for acetone. However, because of the elevated blood sugar and the low carbon dioxide combining power, she was started on intravenous normal saline solution and small doses of regular insulin, 25 units every two hours. Several hours following admission, 5 per cent glucose was added to the intravenous infusions and small quantities of regular insulin were continued. The urinary output remained scant and her blood chemistry studies continued to reveal

the presence of acidosis. The lumbar puncture resulted in bloody spinal fluid with a normal pressure and under normal dynamics. Twelve hours following admission, at which time the blood and urine cultures were reported as positive, large quantities of aqueous penicillin (1,000,000 units every two hours) were administered. When the organism was identified as *A. aerogenes*, 1 gm. of aureomycin was given intravenously every six hours. Later in the afternoon, because of persistent tachycardia and the development of basal râles, she was given digitoxin, without apparent benefit. She remained comatose, became anuric and died without any evidence of improvement.

Autopsy: The arterial embalming was performed prior to the postmortem examination. The significant findings were confined to the following organs: The heart weighed 430 gm. and there were a few epicardial petechial hemorrhages. The right side of the heart, including the valves, was not remarkable; the left ventricular wall was thickened, measuring 18 mm. The mitral valve showed thickening and shortening of the chorda tendinea; there was a 15 mm. friable gray-red vegetation on one valve cusp. The coronary arteries revealed moderate concentric yellow thickening of the intima. The right and left lungs weighed 600 and 550 gm., respectively; they both demonstrated moderately severe pulmonary edema. The blood vessels at the base of the brain revealed patchy atherosclerosis, and no thrombi were detected. The subarachnoid fluid was clear. The right parietal and occipital lobes showed acute infarction. The right and left kidneys weighed 150 gm. each. The right kidney revealed a smooth external surface and one small yellow subcapsular area. All of the papillae were necrotic and there was partial sloughing of several papillae. The necrotic areas were surrounded by red zones. Section of the left kidney demonstrated necrosis of a few papillae but no sloughing. Both renal pelves were hemorrhagic and filled with cloudy urine. There was no demonstrable obstruction in either of the ureters or in the lower urinary tract.

Histologically, the heart revealed moderate coronary atherosclerosis, moderate myocardial hypertrophy and vegetative bacterial endocarditis. The right kidney demonstrated necrosis and infarction of the papillae, several of which had sloughed and separated from the remainder of the kidney parenchyma. Edema and dense leukocytic infiltration extended from the border of the infarcted areas throughout the kidney. In addition, there was a well developed degree of arteriolar nephrosclerosis (figure 3); the glomeruli were essentially normal. The left kidney showed changes similar to the right but with fewer areas of infarction in the renal pyramids. The anatomic diagnoses were acute right encephalomalacia, vegetative mitral valvulitis, septicemia, acute pyelonephritis with acute necrotizing papillitis, pulmonary edema, myocardial hypertrophy and clinical diabetes mellitus.

Case 3. A 72 year old white male was admitted to the urology service of University Hospital on April 26, 1951. He complained of an inability to urinate spontaneously of approximately one week's duration. Two years before admission he had required catheterization for urinary retention, and had had no subsequent difficulty until the present admission. He had noted low back pain, frequency and nocturia during the six months prior to admission. There was no history of hematuria, chills or fever. The past and family histories were not contributory. System review revealed anorexia for a few days prior to admission, and aching pain in both shoulders and in the lower midback for a period of six months.

Physical examination revealed a well developed and well nourished pale white male in some distress because of the inability to void. His temperature was 99° F.; pulse, 88; respirations, 18; blood pressure, 160/70 mm. of Hg. Examination of the skin, mucous membranes, eyes, ears, nose, throat and neck was not remarkable. The thorax was symmetrical and the lungs were clear. The heart was not enlarged but an apical systolic murmur was audible. The abdomen was soft, and a mass was palpable extending from the symphysis pubis to a point just below the umbilicus.

Rectal examination revealed a 4 plus enlargement of the prostate gland; the gland was smooth, nontender and rather hard in consistency. The bones and joints were essentially normal. The neurologic examination was normal. The clinical impression on admission was carcinoma of the prostate gland and acute urinary retention.

The blood count on admission revealed 2,840,000 red blood cells, 9.4 gm. of hemoglobin and 9,300 white cells, with 93 per cent neutrophils. The urine revealed 2 plus albumin, 10 to 15 white blood cells and numerous red cells. The blood urea nitrogen was 122.5 mg. per cent, serum sodium 327 mg. per cent, potassium 24.5 mg.

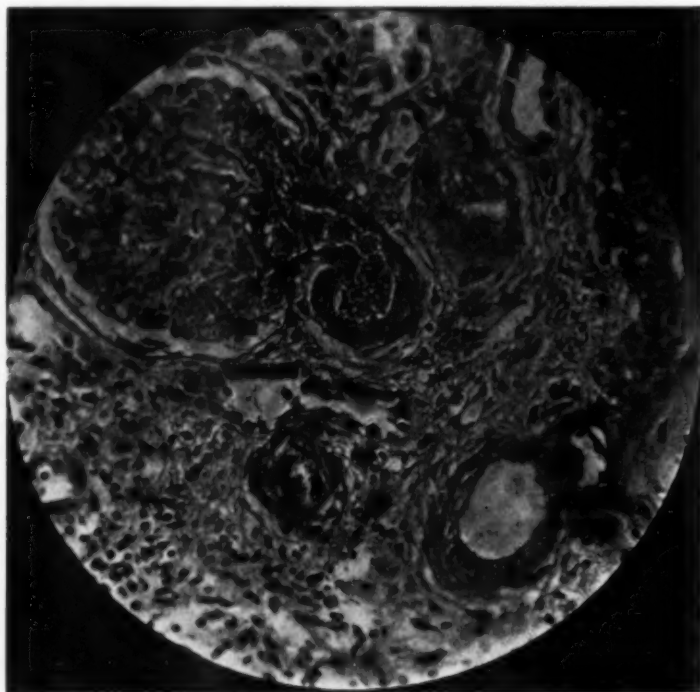


FIG. 3. Case 2. Photomicrograph, representative of the entire kidney, illustrating arteriolar nephrosclerosis of the afferent artery and also demonstrating a relatively normal glomerulus.

per cent, alkaline phosphatase 8.35 units and acid phosphatase 3.8 units. The serologic test for syphilis was negative. The carbon dioxide combining power was 30 vol. per cent. A urine culture resulted in a mixture of organisms with *A. aerogenes* predominating; *E. coli* and *Proteus vulgaris* were also present.

On April 30 the blood urea nitrogen was 136, carbon dioxide combining power 26 vol. per cent and potassium 29 mg. per cent. On May 7 the blood count revealed 1,840,000 red cells, 4.9 gm. hemoglobin and 13,600 white cells, with 97 per cent neutrophils. On the same date the blood urea nitrogen was 52 mg. per cent and the carbon dioxide combining power 79 vol. per cent. On June 6 the blood urea nitrogen was 23, chlorides 511 mg. per cent, potassium 17 and sodium 285 mg. per cent. X-ray

of the chest demonstrated cardiac enlargement and bilateral pleural effusion. A 1 cm. nodule projected over the anterior end of the right fifth rib and was suggestive of metastatic tumor. A flat plate of the abdomen revealed massive metastasis to the left sacroiliac area, and also multiple small metastatic areas in the sacrum and right femur. The electrocardiogram demonstrated myocardial insufficiency.

On admission an unsuccessful attempt was made to catheterize the patient. Because of the possibility of urinary extravasation he was taken to the operating room, where a suprapubic cystostomy was performed under local anesthesia. The urinary bladder was distended and contained numerous clots of blood. A large extensive carcinoma of the prostate gland was noted. Postoperatively the patient was placed on streptomycin, 0.5 gm. four times daily, and stilbestrol in oil, 5 mg. four times daily by the intramuscular route. On April 30 the patient developed moist râles in both lung fields and edema of the hands and face. He was then digitalized and given intranasal oxygen. He was maintained on intravenous fluids, including 1/6 N. molar



FIG. 4. Case 3. Gross section of the right kidney, illustrating papillary necrosis and a dilated pelvis containing a chocolate colored exudate.

lactate and whole blood transfusions. He improved slowly and began taking oral feedings, and his urinary output remained good, averaging 1,000 to 3,000 c.c. daily. On May 11 the patient developed mild icterus, and the van den Bergh revealed a total of 6.25 mg., with a direct positive of 3.68 mg. During this time his temperature ranged from 98.6 to 101° F.; pulse, 80 to 90 per minute; blood pressure, 170 to 190 mm. Hg systolic over 70 to 90 mm. diastolic. His condition remained more or less static until June 1, at which time he began to deteriorate rather rapidly. His blood urea nitrogen began to rise again in spite of an adequate urinary output. At the same time he developed a spiking fever, and became mentally disoriented, and his jaundice became deeper. On June 18 he developed Cheyne-Stokes respiration, and on June 21 his pulse rate rose to over 200 and he died shortly thereafter. Terminally his temperature rose to 105° rectally and his urinary output fell to 500 c.c. on the last hospital day. On June 18 the blood culture was positive for gram-negative rods, later identified as *A. aerogenes*.

Autopsy: The body was embalmed prior to postmortem examination. The important autopsy findings were as follows: The heart weighed 350 gm. and was essentially normal, except for a mild degree of coronary atherosclerosis. The lungs weighed 600 gm. each; they showed patchy bronchopneumonia of the dependent portions of both lower lobes. The liver demonstrated chronic passive congestion and the biliary tract was normal. The right kidney weighed 250 gm. and the left 100 gm. The cortical surface of the right kidney was smooth, and on section (figure 4) the

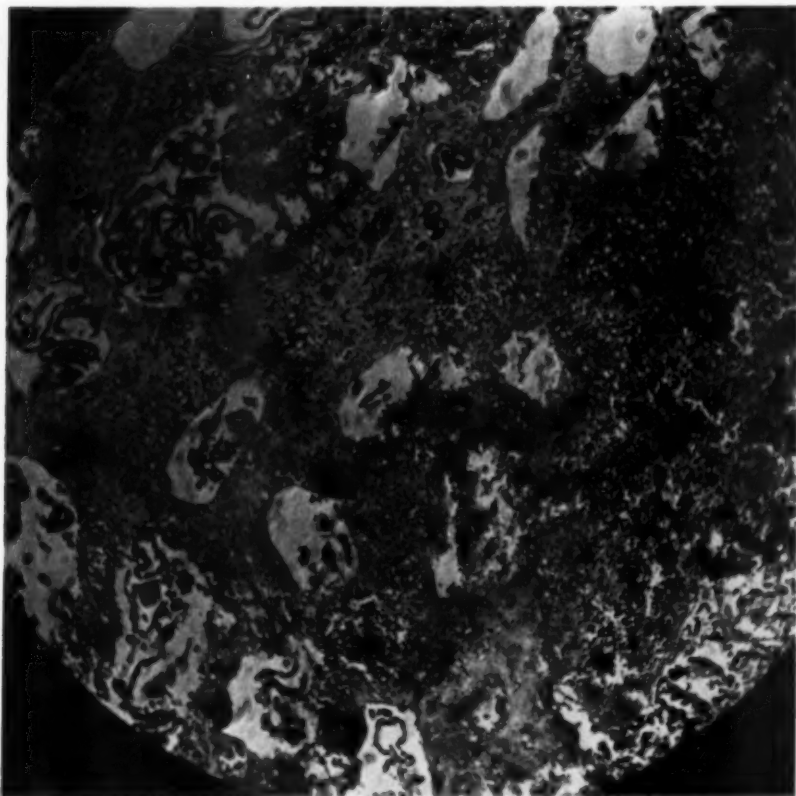


FIG. 5. Case 3. Photomicrograph illustrating an area of coagulation necrosis and the surrounding zone of dense leukocytic infiltration.

typical necrotic papillae were present. The pelvis was slightly dilated and the mucosa was hemorrhagic. The left kidney had an adherent capsule and on section showed a marked dilatation of the pelvis, which contained chocolate colored, purulent exudate. There was no evidence of papillary necrosis in the left kidney. The left ureter was completely obstructed at the bladder wall; no obstruction of the right ureter could be detected. The prostate was three times the normal size, and contained a tumor which had invaded the periprostatic tissues. The sacroiliac joint also contained metastatic tumor tissue.

Histologically, the left kidney showed pyonephrosis, pyoureter and active pyelonephritis. The right kidney (figure 5) showed areas of coagulation necrosis involving the tips of the renal papillae, and many leukocytes were demonstrated. No bacteria could be found in the sections. Surrounding the infarcted area was a zone of edema with many dilated capillaries. There was no evidence of vascular thrombosis in the area of infarction. The remainder of the kidney showed scattered areas of dense leukocytic infiltration, including numerous leukocytes in the tubules. The arteries, arterioles and glomeruli were essentially normal.

The anatomic diagnoses were carcinoma of the prostate with invasion of periprostatic tissue, obstruction of the left ureter and metastasis to the sacroiliac region, left pyonephrosis, pyoureter and pyelonephritis, necrotizing papillitis of the right kidney, bronchopneumonia both lower lobes, and post-transfusion icterus.

DISCUSSION

As can be discerned from a review of the literature and from the details of the cases presented, there are no hard and fast diagnostic criteria with regard to this disease. A correct antemortem diagnosis is rarely made; one of our three cases (case 2) was correctly diagnosed prior to death. We have become so conscious of this illness that on several occasions we have made a clinical diagnosis of necrotizing renal papillitis, only to have it disproved at autopsy. Only by means of an awareness of its possibility and a recognition of the more common symptoms can more accurate clinical diagnoses be made in the future.

The disease should be considered as a diagnostic possibility when any of the following situations present themselves: (1) patients with diabetic acidosis in whom the diabetes is brought under control, but the pyuria, bacteriuria and uremia become progressively worse; (2) patients with foci of infection elsewhere who suddenly develop signs of severe renal infection; (3) patients with urinary tract obstruction who develop rapidly fulminating renal infection; (4) any diabetic patient with a mild urinary sepsis in whom the infection suddenly becomes worse; (5) patients with long standing pyelonephritis in whom the infection suddenly increases in severity.

It is important to bear in mind the frequency with which diabetic patients have asymptomatic pyuria and bacteriuria. As stated previously, such mild infections may be the precursor of fulminating necrotizing papillitis. In view of these facts it seems only logical that the physician, in routinely examining the urine of his diabetic patients, should check for bacteria and cells as well as for sugar and acetone. If cells and bacteria are present, the sediment should be stained to identify the specific organism. Also, if the bacteria appear in repeated specimens, or are present in large quantities, the urine should be cultured.

To date, there are very few reported cases of healed lesions in this particular infection. The mortality rate is thus extremely high.

The etiology of this lesion still remains uncertain. The three cases which we have presented seem to offer some challenge to the etiologic factors formerly proposed. In case 1, there was no focus of infection elsewhere

in the body and also no evidence of obstruction in either the upper or the lower urinary tract. This patient did not have diabetes, and at autopsy there was no evidence of any pronounced vascular lesion in the kidneys. In case 2, the patient had been an uncontrolled diabetic for at least several years, and although there was no history of urinary infection, certainly one could not eliminate this as a possibility. This latter patient was not under the care of a physician prior to hospitalization, and a minor urinary infection could have existed without presenting major clinical symptoms. At autopsy this patient likewise had no evidence of obstruction in either the upper or the lower urinary tract. However, her infection was so virulent as to result in septicemia and an acute vegetative endocarditis. Case 3 presented some very interesting findings and also several incompatibilities which defy explanation on the basis of all etiologic factors previously proposed. This patient had a carcinoma of the prostate with resulting obstruction of one ureter at the bladder wall. However, the necrotizing papillitis occurred in the opposite kidney, where no ureteral obstruction existed. We are unable to explain this rather strange sequence of events in the latter case.

Only one of our patients had clinical diabetes, and the other two did not relate a history or demonstrate findings compatible with diabetes. Thus we wish to reemphasize that the necessary relationship of diabetes to the pathogenesis of this condition is far from being established at this writing.

Intravenous and retrograde pyelograms should be performed whenever this lesion is suspected and wherever the conditions permit. In a significant percentage of cases a diagnosis can be established or confirmed by means of this procedure. Some of the classic findings are: (1) deformity of the tips of the calyces; (2) dilatation of the tips of the calyces; (3) sloughing of the tips of the papillae; (4) communication by means of small channels between the calyces and the pelvis. A number of the roentgen findings described resemble those often seen in renal tuberculosis.

The therapeutic approach to this problem concerns itself with prophylaxis as well as treatment of the active infection. All urinary infections, especially in diabetics, should be adequately treated. With the availability of the wide spectrum antibiotics, it is more than ever essential to identify the specific organism. In resistant infections it is important to determine the sensitivity of the causative organisms to the various antibiotic or chemotherapeutic agents. Although a few cases, described in the literature, have been treated by means of antibiotics, the great majority have been treated by either chemotherapeutic agents or urinary antiseptics. All three of our cases received one or more of the wide spectrum antibiotics and failed to demonstrate any appreciable response to these agents. However, since we did not recognize the necessity, sensitivity tests were not performed and we are not in a position to state whether the individual organisms, detected on either blood or urine culture, were amenable to the antibiotics used in each specific instance.

Most authors, and many physicians with whom we have discussed this problem, are still of the opinion that this is a fulminating type of pyelonephritis. Although we are unable to afford a better explanation at this time, we still do not entirely agree with this concept. We have seen many examples of acute and chronic pyelonephritis at post mortem, in both diabetic and nondiabetic patients, with and without urinary obstruction. However, only in the three cases described in this report did necrotizing renal papillitis make its appearance. If this lesion results from or is secondary to acute pyelonephritis, why does it not occur more frequently? The urology service encounters many instances of prostatic hypertrophy with obstruction, resulting in secondary hydro-ureter and hydronephrosis. An appreciable number of these latter cases are complicated by pyonephrosis and yet do not develop necrotizing papillitis. This disease is reported to be more common in diabetic individuals, and certainly the incidence of urinary tract infection is quite high in such patients. Why then, in the presence of a high incidence of clinical diabetes and associated urinary infections, is necrotizing papillitis such a rare occurrence? These questions, of course, cannot be adequately answered. It is our hope that interest in this condition will be stimulated and that further investigation may solve the problem. A more accurate correlation between the clinical features and the pathologic findings may serve to clarify the etiologic background of this disease.

SUMMARY AND CONCLUSIONS

Three cases of necrotizing renal papillitis are presented from both the clinical and pathologic viewpoints. In one instance the lesions occurred in an uncontrolled diabetic patient who developed a septicemia, acute vegetative endocarditis and cerebral embolism. In the remaining two cases, the patients were nondiabetics and demonstrated no evidence of urinary obstruction with regard to the involved kidneys.

We are not in complete accord with all previous opinions suggesting that this lesion is a fulminating type of pyelonephritis. We do not dispute this possibility, but we are unable to explain the relatively low incidence of necrotizing papillitis in light of the relatively high incidence of acute pyelonephritis.

It has been emphasized by many authors that this disease, in nondiabetic subjects, is usually associated with urinary tract obstruction. Case 3 offers reason for doubt with regard to the above explanation. This patient had a carcinoma of the prostate which, in the process of its extension, completely obstructed the left ureter at the bladder wall; the right ureter remained patent throughout its course. However, it was the right kidney and not the left which demonstrated necrotizing renal papillitis. Obviously obstruction alone does not afford an adequate explanation for this lesion.

Except for the rarity of vascular lesions, our pathologic findings are in agreement with those of other investigators. We were strikingly impressed

with the relative absence of significant vascular lesions in both the diabetic and the nondiabetic subjects. Our diabetic patient failed to demonstrate any lesions characteristic of the Kimmelstiel-Wilson syndrome. In addition, the involved kidneys did not demonstrate evidence of any long standing pyelonephritic process.

Antemortem diagnosis of this lesion is possible, if only one considers its possibility and is familiar with the clinical symptoms which the disease presents. It behooves one to suspect this disease when dealing with non-diabetic as well as diabetic patients who develop acute renal insufficiency. It is especially important to suspect the lesion in diabetic patients in whom the diabetes is controlled but the symptoms of renal failure become progressively worse.

With the advent of the ever increasing number of wide spectrum antibiotics, we feel that it is more imperative than ever before to recognize and to be familiar with this condition. Although the mortality rate has approximated 100 per cent in the past, it is entirely possible that in the future many of the newer agents will be capable of controlling renal infection and preventing terminal necrotizing renal papillitis.

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PERFORATION OF THE INTERVENTRICULAR SEPTUM FOLLOWING MYOCARDIAL INFARCTION *

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INTRODUCTION

RUPTURE of the interventricular septum following myocardial infarction was first described over a century ago. Sager¹ in 1934 found 17 cases in the literature and described one of his own. He pointed out the criteria needed for the diagnosis of this condition, namely, the sudden onset of a loud precordial systolic murmur and thrill in a patient with recent myocardial infarction. The reviews of Weber,² Fowler and Failey³ and Bickel and Mozer⁴ pointed out the findings in 39 additional cases. Numerous authors^{5-18, 20} have described other cases, bringing the total number to 88 in the available literature.

Rupture of the interventricular septum occurs more frequently than the scattered reports above would indicate. We have seen the five cases described herein during the past four years. Edmondson and Hoxie¹⁹ found 13 cases of septal rupture, occurring within 17 years at the Los Angeles County Hospital. As many as four cases have been reported by Bickel and Mozer,⁴ Garlick and Hughes¹³ and Nareff et al.⁹ Garlick and Hughes saw all four of their cases within a period of one year. Ruptures of the septum are often hidden beneath postmortem blood clots, and if the septum is not adequately exposed and washed at postmortem examination a tear can be easily missed. On the basis of Edmondson and Hoxie's report,¹⁹ it is probable that septal rupture accounts for 1 to 2 per cent of the deaths following myocardial infarction. By comparison it has been shown by Bean⁵ that 9 per cent of deaths following recent myocardial infarction are due to rupture of the ventricular wall, but most of these are ruptures of the left ventricular wall with cardiac tamponade.

Antemortem diagnosis of rupture of the septum following infarction has been made in about one-fourth of the reported cases. The diagnosis is not difficult as long as one is aware of the salient clinical features. In all five of our cases the diagnosis was made before death. Four of these cases were studied at autopsy. The fifth was typical of this condition and, although

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autopsy was not obtained, the clinical features were classic. This case is included in this report.

This paper will describe in some detail the five cases we have seen. With the available data in 93 cases, we will discuss the clinical features of this syndrome, the differential diagnosis and the poor prognosis in such cases.

CASE REPORTS

Case 1. This 64 year old white male became ill on November 10, 1947, with severe epigastric pain, nausea and vomiting. He had a past history of angina pectoris for four years and rather marked hypertension for about 10 years. On admission to the hospital no murmurs were heard. The blood pressure was 218 mm. Hg systolic and 110 mm. diastolic. The aortic second sound was greatly accentuated. An electrocardiogram showed only left axis deviation. The following day he left the hospital against advice. He remained in bed at home for only one day. While walking uphill the next day, 72 hours after the original attack, he developed severe crushing substernal pain which radiated into the neck and both shoulders, and out both arms. The pain was associated with nausea, severe sweating, pronounced dyspnea, cyanosis and coldness of the extremities. He was re-admitted to the hospital. The pulse rate was 130; the respiratory rate was 30. The blood pressure was now 100 mm. Hg systolic and 80 mm. diastolic. There was now present a grade IV to grade V systolic murmur, accompanied by a pronounced systolic thrill, both most marked in the second and third interspaces at the left sternal border. Electrocardiogram on November 13 showed the presence of bundle branch block. The lungs remained clear until shortly before death, which occurred suddenly on November 21. The final clinical impression was coronary occlusion with myocardial infarction involving the interventricular septum and subsequent rupture of the septum.

At postmortem examination the heart weighed 600 gm. The myocardium showed no changes except in an area high on the septum, where the color was mottled brownish red and the wall was thinner than that elsewhere in the septum. Through this area a stellate perforation had occurred at a point approximately 2 cm. below the aortic valve and 1.5 cm. from the anterior margin of the septum (figure 1). The tissue bordering the perforation was only 1 mm. in thickness, with roughening about its borders. A thrombus was present in the right auricular appendage. Microscopically, the infarcted area showed disappearance of the myocardial fibers, with infiltration of many mononuclear phagocytes and proliferation of the muscle sheath cells. No occlusion of any of the coronary arteries was demonstrated either grossly or microscopically, though they were narrowed by sclerotic plaques. Other changes found at autopsy consisted of pulmonary edema, bilateral hydrothorax, congestion and central lobular necrosis in the liver, severe arteriosclerosis of the aorta and vascular scars of the kidneys.

Case 2. This 63 year old white male diabetic, with a history of vague substernal constriction on exertion for the preceding month, had an attack of severe substernal pain which occurred while he was chopping wood and lasted about one and a half hours. He was admitted to the hospital a day later, when slight cyanosis of the skin and nail beds was noted. His blood pressure was 124 mm. Hg systolic and 80 mm. diastolic. Auscultation of the heart was negative except for an occasional premature beat. Electrocardiograms showed the typical changes of a recent posterior myocardial infarction. On the day of admission he experienced mild precordial pain and dyspnea. The following day the second heart sound was replaced by a distinct friction rub which occupied late systole and the greater part of diastole. A few râles were heard at the base of the right lung. In the evening of the same day the friction rub had disappeared and in its stead there was a grade V systolic murmur, loudest in the fourth

intercostal space just to the left of the sternum. This murmur could be heard over the entire precordium and at the inferior angle of the left scapula. A pronounced systolic thrill was palpable at the left border of the sternum, best felt in the fourth intercostal space. The patient's systolic blood pressure had now fallen to 80 mm. of mercury and the diastolic pressure was unobtainable. A diagnosis was made of rupture of the interventricular septum following its infarction. The following day numerous râles appeared at the lung bases. On the fourth hospital day his blood pressure became unobtainable and he died quietly. The clinical diagnosis was rupture of the interventricular septum following acute myocardial infarction.

At postmortem examination the heart weighed 550 gm. There was dilatation of both ventricles and hypertrophy of the left. Softening and reddening of the



FIG. 1. Case 1. View of septal rupture which has occurred high in the anterior portion of the septum.

posterior wall of both ventricles and of the posterior one-half of the interventricular septum was found near the apex. There was a large perforation 2 cm. in diameter in the septum along its posterior margin near the apex (figure 2). The coronary arteries were moderately sclerotic throughout, with lipoid and calcific deposits. Thrombosis, with complete occlusion, had occurred at the site of one of these plaques in the right coronary artery 2.5 to 3 cm. from its origin. The peritoneal and pleural cavities were free of fluid. Congestion and edema of the lungs, congestion and central lobular necrosis of the liver, and congestion of the kidneys were present at autopsy.

Case 3. This 49 year old white female, with a past history of hypertension, angina pectoris and chorea with rheumatic fever, entered the hospital on August 25,

1949, two days after the onset of severe substernal pain which radiated down both arms. Since the onset of the pain she had been anorexic and had noted cold and clammy extremities. An electrocardiogram prior to admission showed changes characteristic of acute anterior myocardial infarction. Examination of the patient showed a blood pressure of 130 mm. Hg systolic and 90 mm. diastolic, a temperature of 102° F., a pulse rate of 120 and a respiratory rate of 18. The heart sounds were distant. A very faint aortic systolic murmur was heard. Early in the morning of her second hospital day she had another episode of substernal pain which radiated into the left arm. Her blood pressure dropped to 80 mm. Hg systolic and 70 mm. diastolic. The patient appeared to be in a state of collapse. Auscultation of the heart now revealed a



FIG. 2. *Case 2.* View of septal rupture which has occurred in the apical portion of the septum.

loud, rough systolic murmur, loudest in the fourth intercostal space 3 to 4 cm. to the left of the midsternal line. This murmur grew louder during the next few hours. A pronounced systolic thrill was felt and was most intense at the point where the murmur was loudest. Electrocardiograms showed evolutionary changes of anterior myocardial infarction. On the tenth hospital day she developed pulmonary râles, and distention of the neck veins appeared. On the seventeenth day the patient became cyanotic and semicomatose. By the twenty-third day marked congestive failure was present, and this persisted until she suddenly died on the forty-sixth hospital day.

The final clinical impression was rupture of the interventricular septum following the infarction. Permission for autopsy was not granted.

Case 4. This 64 year old white male was admitted to the hospital on May 8, 1951, following an episode of rather severe substernal pain radiating into both arms. Electrocardiograms showed evidence of infarction of the anterior portion of the left ventricle. He did well until May 17, when his blood pressure was found to be 90 mm. Hg systolic and 80 mm. diastolic. On this day there appeared an extremely loud systolic murmur, not present before, which could be heard over the entire thorax but best in the third left interspace at the sternal border. At this time the patient experienced general malaise, anorexia and fatigue. He became more critically ill, and by May 28 there were moderate cyanosis and livor mortis about the neck and upper thorax. Modified Cheyne-Stokes breathing was present. There was extreme engorgement of the neck veins, which were tense with blood and did not pulsate. The lungs were clear. The heart rhythm was regular; its rate, 100. A distinct systolic thrill was palpable in the third intercostal space at the left sternal border. A grade V high pitched harsh systolic murmur was heard at the left sternal border, and was also audible over the entire thorax and upper abdomen. The liver was markedly enlarged. The patient did not respond to mercurial and aminophylline therapy, and died on May 30 after a day of delirium and somnolence. The final clinical impression was ruptured interventricular septum following infarction.

At postmortem examination the heart weighed 370 gm. The epicardial surface was covered by a thick layer of fibrin. The apical one-third of the left ventricle was softened, thin and fibrotic. The entire area of change was approximately 6 cm. in diameter and involved the anterior three-fourths of the septum, which was thin and friable and bulged into the right ventricle. A ragged irregular perforation 8 mm. in diameter had occurred near the center of the involved area in the anterior one-half of the septum. The endocardium about the perforation was roughened, and the myocardium discolored and hemorrhagic. The coronary arteries contained many plaques of lipoid and calcific material, with marked narrowing of the lumen. A thrombus occluded the anterior descending branch of the left coronary artery between two of these narrowed areas.

Case 5. This 61 year old white female, with a previous history of hypertension and two "strokes" within the past seven years, was admitted to the hospital on December 10, 1950, several hours after the onset of substernal pain. Examination revealed a grade V systolic murmur in the "mitral" area and a questionable diastolic murmur in the same area. There was mild hepatomegaly and bilateral Babinski's signs. The electrocardiogram showed changes consistent with anterior myocardial infarction. The patient was placed on Dicumarol therapy, but this was stopped because of vaginal bleeding. On December 20 she developed another episode of chest pain and went into peripheral circulatory collapse. The loud systolic murmur persisted in the mitral area, but now was also heard in the aortic area and along the left sternal border. Her blood pressure fell. She developed generalized edema and became anuric. She had been treated with oxygen, Mercuhydrin, Dilaudid and intravenous fluids. Her respirations became shallow and she died on December 30. The final clinical impression was anterosseptal myocardial infarction with rupture of ventricular septum.

At postmortem examination the heart weighed 440 gm., with hypertrophy involving mainly the left ventricle. There were partial calcification of the mitral annulus fibrosus and slight calcific stenosis of the aortic valve. Arteriosclerosis of the coronary arteries was moderately severe, with thrombosis and occlusion of the anterior descending branch of the left, and of the right coronary artery at a point 3 cm. from its origin. The apical one-third of the interventricular septum was softened and scarred, with a thin area 3 cm. in diameter near the apex. Through this area a ragged perforation 2 by 1 cm. was found. A zone of fibrin deposition surrounded it but no mural thrombus could be found. The zone of more recent infarction in-

volved the apical one-fourth of the left ventricle. Microscopically, many foci of scarring were found throughout the myocardium. Other changes consisted of severe generalized arteriosclerosis, ascites, pericardial and pleural effusions, with congestion and centrilobular necrosis of the liver, and necrosis of the renal tubules. Numerous small infarcts were found in the spleen.

DISCUSSION

These five cases well illustrate the criteria needed for the diagnosis of rupture of the interventricular septum following infarction of the heart. To make the diagnosis, one should first have evidence clinically that myocardial infarction has taken place. This should be followed by the sudden appearance of a loud systolic murmur, heard best in the third and fourth intercostal spaces just to the left of the sternum, but usually audible widely over the precordium. The murmur is frequently accompanied by a systolic thrill, greatest in the area where the murmur is loudest.

Many of the data on previously reported cases are sketchy. We have taken the clinical and pathologic findings in the reports of others and our own, and have attempted a clinical and statistical analysis of the available data to give a comprehensive picture of this syndrome.

Age and Sex: The average age of these patients with septal rupture (available in only 66 cases) was 61 years, the youngest being 35 and the oldest 87 years. Only eight of the patients were under 50 years of age. These figures compare well with ages of patients having their initial myocardial infarction; Bean²⁰ in his series reported an average age of 61.

In patients with rupture of the septum following myocardial infarction the sex was given as male in 43 cases (66 per cent) and female in 22 (34 per cent). The percentage of females here is higher than in statistics of sex incidence in acute myocardial infarction alone, where only 13 to 14 per cent were females in the series of Bland and White²¹ and Parkinson and Bedford.²²

Hypertension: At least 27 of the patients with septal rupture either had a past history of hypertension or the blood pressure was found elevated during their terminal illness. Bean²⁰ reported that 81 of the 179 cases of myocardial infarction had a history of previous hypertension. Elevation of the left ventricular pressure does not seem to be the only condition which increases the likelihood of septal rupture after infarction, although theoretically one would suppose that it might be a definite contributing factor. The main factor here is similar to that of rupture in any portion of the ventricle, namely, the extent of the necrosis of the ventricular wall.

Murmurs: In 67 of these cases the physical findings in the heart were reported. A loud systolic murmur was stated to be definitely present in 65 of the patients, but in two cases no murmur was heard. Weber² discusses a case reported by Bickel and Mozer in which the septal defect was 2.0 by 0.5 cm. but in which no murmur could be heard. Although no explanation could be given for the absence of the murmur, it seems quite likely that this situation was analogous to that of a very large congenital defect of the inter-

ventricular septum in which the defect was so great that the mechanical factors necessary for the production of a murmur were not fulfilled. Frequently, the smaller the defect the louder the murmur. Diastolic murmurs have been reported in only four patients, and all of these had evidence of marked congestive heart failure with pronounced cardiac dilatation.

Thrill: Commonly, a systolic thrill develops following the rupture of the interventricular septum, and in the cases reviewed it was present in 30 and stated to be absent in 10. Two of the 10 cases in whom the thrill was not felt were patients in whom a systolic murmur was not heard. Actually, the production of the thrill is dependent more or less on the factors necessary to produce the systolic murmur. Both the thrills and the murmurs should of course be carefully timed by palpation of the carotid pulse while ausculting the heart, since such pronounced signs in diastole, rather than systole, may be due to rupture of an aortic cusp, partial rupture of the aorta or dissecting aneurysm of the aorta.

Sudden Changes in Symptoms and Physical Signs: The majority of the cases showed a precipitous change in the patient's clinical status coincidental with the development of signs of rupture of the interventricular septum. In 24 patients there was a definite renewal or aggravation of the cardiac pain, and in 10 additional patients there was moderate increase or return of pain. Promptly following the rupture of the septum, 34 patients developed marked dyspnea at rest, 39 had frank congestive heart failure, and 27 either became precipitously cyanosed, or previous cyanosis became more pronounced. In general, one may conclude that the physical signs in the heart are those as described by Roger in congenital patency of the interventricular septum. It is important to have good initial observation and recording of the heart sounds prior to the rupture so that the precipitous changes may be readily appreciated.

Location of the Rupture: Although these perforations of the interventricular septum are found most frequently in the muscular portion near the apex of the heart, they may occur at any point. In three cases there have been double perforations of the septum; one case had three perforations (Bayley and Fader), and one case had four perforations (Weber).

Time of Onset After Infarction, and Prognosis: In 35 of the cases one could ascertain with reasonable accuracy the time that elapsed from the onset of symptoms of the myocardial infarction until rupture of the septum occurred. This was found to vary from a minimum of four hours to a maximum of one month. In only five of these cases was the time interval over 10 days. Once rupture of the septum has occurred, the prognosis in such patients is extremely poor. Thus, in 67 patients the duration of life was as follows: 40 survived less than one week, 21 survived from one to eight weeks, and only five lived longer than eight weeks. One patient survived for nearly five years.²³ It is obvious, therefore, that the prognosis in myocardial infarction which results in perforation of the interventricular septum

is far graver than in myocardial infarctions in general. Bland and White²¹ reported that 81 per cent of 200 patients with acute myocardial infarction were living at the end of one month, with 25 per cent surviving at the end of 10 years. These figures, of course, are in direct contrast to those stated above in patients with perforation of the interventricular septum due to myocardial infarction.

Treatment: The treatment of patients with septal rupture following infarction is primarily the same as that for patients with infarction alone. Congestive heart failure is frequent, and digitalis, mercurial diuretics and a low sodium diet are all indicated. However, all measures are usually unavailing.

Differential Diagnosis: The diagnosis of rupture of the septum following myocardial infarction is not difficult as long as one is aware of this complication and follows the patient with frequent examinations. In any patient with evident infarction, the appearance of a loud precordial systolic murmur may be due to relatively few things: a pericardial friction rub, insufficiency of the mitral valve, rupture of a papillary muscle, or rupture of the septum.

In two of our cases the abnormal sound at onset was interpreted as being a pericardial friction rub. It was heard in both systole and diastole and had a distinct "rubbing" character. This sound was probably actually due to pericarditis associated with the myocardial infarction. Within 24 hours, however, this initial "rub" was definitely replaced with a loud, harsh, high-pitched systolic murmur. About 14 per cent of patients with acute myocardial infarction develop audible friction rubs.²⁰ The sounds of such rubs are usually scratchy, they usually have a diastolic as well as a systolic component, and they are much softer and more evanescent than the murmur of septal rupture.

Relative mitral insufficiency may occur with development of cardiac failure and dilatation of the left ventricle. This will also produce a systolic murmur. About 38 per cent of patients with acute infarction have such murmurs.²⁰ This murmur is less intense and is lower pitched, and is located nearer the apex than the systolic murmur heard in septal rupture. The systolic thrill is also less evident, and is usually absent in such patients.

Rupture of a papillary muscle is rare, with only about 25 cases recorded as late as 1944.²⁰ According to Bailey and Hickam,²⁰ 12 of these patients had adequate reports of examination of the heart prior to death. Four of these patients had a systolic murmur only, and three had both systolic and diastolic murmurs. The systolic murmur is loud and of maximal intensity at the apex. The location of the murmur might serve to differentiate this condition from septal rupture. Otherwise this condition is very similar clinically, as it nearly always follows acute myocardial infarction, and such patients show peripheral circulatory collapse, pulmonary edema and syncope, and survive only a few hours or days following the catastrophe.

There is, in addition, a group of conditions not associated with infarction that may give murmurs quite similar to those heard in patients

with septal rupture. A congenital septal defect would give a similar murmur and thrill, but, in general, such patients are in a younger age group; they have other stigmata of congenital heart defects; the murmur, of course, is not sudden in appearance, and there is usually no evidence of infarction of the myocardium. Rupture of mitral chordae tendineae may occur in patients with deforming rheumatic valvulitis and those with subacute bacterial endocarditis. In this condition, described in detail by Bailey and Hickam,²⁶ there is the sudden appearance of a typical murmur which is loud, usually harsh or coarse, precordial, maximal at the apex or along the left sternal border, and systolic in timing. Occasionally these patients also have low pitched apical diastolic murmurs. The systolic murmur is usually accompanied by a thrill. Atrial fibrillation sometimes ensues, and cardiac failure is prone to occur after a number of months or years. Such patients have a better prognosis than those with rupture of the infarcted septum, and they may be distinguished from the latter by their other findings, suggestive of underlying rheumatic heart disease or subacute bacterial endocarditis. In a rare case of subacute bacterial endocarditis, the myocardium of the septum may become involved to a point where it ruptures. This produces a picture identical to that found in rupture after infarction,²⁶ except that here again one should have definite evidence of the existence of bacterial endocarditis.

Two other congenital defects may rarely give rise to murmurs and thrills that simulate septal rupture following infarction. A congenital fibrous aneurysm of the membranous portion of the septum may rupture and produce these effects.²⁷ Aneurysms of the sinus of Valsalva may dissect down the septum and rupture into the right ventricle. This usually occurs in early adult life (14 to 30 years) when it is due to a congenital lesion, and somewhat later when due to syphilis. Here the murmur and thrill occur not only in systole but also in diastole; it is maximal at the third and fourth intercostal spaces along the left sternal border, and seems to originate from a superficial portion of the heart. It produces pain, dyspnea and wide pulse pressure, and leads to enlargement of the heart and failure.²⁸

SUMMARY

Five cases of rupture of the interventricular septum following myocardial infarction are presented, four with autopsy study. These cases illustrate the typical clinical features of this process, namely, the appearance of a loud, precordial, systolic murmur and accompanying thrill in patients with acute myocardial infarction. Either there has been no murmur before, or a new, different systolic murmur and thrill along the left sternal border suddenly develop. The septal rupture was recognized shortly after its occurrence in each case. Recognition of rupture of the interventricular septum is important because of the poor prognosis which it bears in patients with myocardial infarction.

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NATURAL HISTORY OF LUPUS ERYTHEMATOSUS DISSEMINATUS *

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INTRODUCTION

THE new vistas opened by the advent of cortisone and corticotrophin in the treatment of lupus erythematosus disseminatus (LED) emphasize the importance of an understanding of its natural history in evaluating therapeutic results critically. A great many isolated case reports have appeared, but these have seldom been collected and there has been a relative dearth of information recorded concerning the disease over a period of time, particularly from onset to death. In the past 15 years, 44 patients have been observed at this institution who have been followed for a reasonable period of time; an additional 279 patients have been collected from the literature as reported during the years 1948-1952.¹⁻²³ These do not represent all patients reported in this period, as some have not been suitable for use in this study because of the paucity of pertinent data, and other cases may have been overlooked. Investigation of these 323 patients affords an indication of the expected course of the disease without the therapeutic use of potent anti-phlogistic agents, and provides a view of its protean clinical features. These cases have not been divided into acute and subacute categories since it is our feeling, in agreement with others,²⁴ that LED varies only in rapidity and severity of onset; to classify the disease in this manner serves only to state the truism that sicker patients have a graver prognosis.

The criteria³ for the diagnosis of LED have been given as (a) erythematous skin lesions, (b) constitutional symptoms of cachexia, fever and weight loss, (c) negative blood culture, (d) arthralgia, (e) renal disease, (f) suppression of blood-forming elements with leukopenia, anemia and thrombocytopenia, (g) adenopathy, (h) nonbacterial endocarditis, (i) serous membrane effusion—pericardial, pleural and peritoneal, and (j) a greater incidence in females. If all these criteria were required to make the diagnosis of LED, it would rarely be made early in the course of the disease or, indeed, even ante mortem. Frequently the diagnostic impression of LED, in the absence of a positive LE cell preparation, is one of retrospective consideration following prolonged observation. In the two series reported here—that from the Columbia-Presbyterian Medical Center (CPMC), and that collected from the literature—at least seven of the 10 diagnostic criteria have been met.

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LED has been variously said to be totally unrelated²⁵ or to bear a close relationship to discoid lupus.²⁶ In a series of 96 patients with chronic lupus reviewed by Wilson and Jordon,²⁶ it was found that patients with chronic discoid lupus might be translated into acute or subacute LED at any time, incident to sun exposure, x-ray, ultraviolet irradiation, treatment with gold, or chronic infection. In these patients, the chronic skin lesions preceded subacute disseminated lupus erythematosus in 26 per cent and acute lupus erythematosus in 20 per cent. In acute cases, arthritis, pleuritis and other complaints might long precede the appearance of the skin lesions.⁴

SIGNIFICANCE OF THE "LE" CELL

Despite the fact that all patients of the present series were chosen from the era prior to the recognition of LE cells, the importance of its diagnostic significance makes its consideration necessary in any discussion of this disease. The "lupus cell" was first described as appearing in bone marrow preparations of 25 patients with LED by Hargraves, Richmond and Morton,²⁷ and has subsequently been the object of extensive and intensive investigation.^{10, 27-45} The appearance of LE cells continues to be relatively specific in active systemic LED^{27, 30} and has not been found in association with the other so-called collagen diseases,^{10, 28, 35} or in normals. False-positive reactions have been reported rarely,^{8, 38, 41, 44, 45} and the high incidence of positivity of the LE cell in LED has been stressed.^{10, 27, 30, 32, 33, 35, 36, 42}

The diagnostic significance of this test now seems apparent. Where it is positive, a diagnosis of LED can be made with a good degree of assurance, but where it is negative, as has occurred on repeated trials in even some acute cases, the diagnosis is not excluded.

GENERAL CLINICAL FEATURES

As previously stated, data are presented concerning a total of 323 patients, 44 followed at the CPMC and 279 collected from the literature. In some of the reports from the literature, all pertinent information is not available; hence, the data presented will be based in some instances on less than the total number reviewed. Where this occurs, special mention of this fact will be made. The data reviewed are summarized in table 1, which gives the incidence of the various symptoms in the present series and the total incidence of these findings in the group of patients, including the CPMC series and those collected from the literature. In the discussion that follows the former will be referred to as Group A; the total—the CPMC series, plus those from the literature—as Group B. Similarly, table 2 summarizes the incidence of physical signs as they occurred in Group A and Group B.

Sex, Race and Age: The disease is predominantly seen in females: Group A, 98 per cent; Group B, 85 per cent. It is not confined to the white race, since 25 per cent of Group A were of the pigmented races (10 Negroes and one Japanese), and in Group B, the incidence in Negroes was 9 per cent,

TABLE I
Incidence of Symptoms

Symptoms	Group A* (per cent)	Group B† (per cent)	(no. of pts.)
Weight Loss	100	—	—
Malaise	100	—	—
Joint Symptoms	77	76	(302)
Gastrointestinal Complaints	36	26	(168)
Abdominal Pain	22	17	(168)
Nausea, Vomiting or Diarrhea	18	13	(168)
Genitourinary Symptoms‡	18	8	(168)
Raynaud's Phenomena	16	8	(168)
Psychoses	9	5	(216)
Convulsions	7	9	(216)
Hemiplegia	2	2	(216)

* Group A includes 44 patients.

† Group B includes 323 patients. If fewer could be used, total number in parentheses after percentage.

‡ Nocturia, irregular menses, amenorrhea.

equal to the percentage of Negroes in the general population in the United States.⁴⁶ In Group A, the age of onset varied from five and one-half to 60 years, but the peak incidence (84 per cent in Group A and 75 per cent in 209 patients of Group B) was in the second, third and fourth decades, with an approximately equal distribution in each decade.

Family History: It is interesting to note that only three of the Group A patients had a family history of rheumatic disease and, in these, two had a history of rheumatic heart disease, rheumatic fever or rheumatoid arthritis in two members of their immediate family. This feature has not been

TABLE II
Incidence of Physical Signs

Physical Signs	Group A* (per cent)	Group B† (per cent)	(no. of patients)
Females	98	85	—
Fever	95	99	(216)
Skin Rash	68	84	—
Ulcerative Lesions—Mouth	18	15	(193)
Cardiac Manifestations	70	68	(214)
Enlarged Heart	34	15	(214)
Murmurs	55	24	(214)
Pericardial Effusion	16	8	(214)
Pericarditis‡	23	21	(214)
Hypertension	18	9	(214)
Pleural Effusion	39	29	(216)
Pleural Rub	20	—	—
Pneumonitis	20	—	—
General Glandular Enlargement	37	32	(216)
Hepatomegaly	29	12	(168)
Splenomegaly	27	17	(168)
Peripheral Edema	25	13	(168)
Facial Edema	12	8	(168)
Eye-ground Changes	20	—	—

* Group A includes 44 patients.

† Group B includes 323 patients. If fewer could be used, total number in parentheses after percentage.

‡ Recognized clinically, by x-ray or by electrocardiogram.

evaluated in the total group, since no reference is made to it in most reports reviewed.

Past History: Review of the histories of past illness revealed no relationship of onset of the disease to an upper respiratory infection. Two of the four children in Group A gave histories of a common allergy: asthma beginning at age three in one, and eczema and angioneurotic edema from the age of six weeks in the other. In two instances a history of hay fever was obtained. A personal previous history of rheumatic disease was observed in only one patient, who gave a 15 year story of malaise and arthritis prior to the onset of the acute episode. Here again, adequate information on the total group is unavailable.

Possible Precipitating Factors: Sensitivity to sun exposure played a rôle in 12 (27 per cent) of Group A. This occurred prior to skin eruption in nine and intensified a preëxisting eruption in three patients. In six of these patients, the sun exposure occurred prior to the onset of any symptoms of the disease.

The exact rôle of emotional upset as a precipitating factor in a disease is difficult to evaluate. Nine (20 per cent) of the patients in Group A gave histories of emotional trauma of various types, including broken marriages, unhappy love affairs or recent deaths in the family. Although there was a history of the use of sulfonamides or antibiotics in many patients, there was no evidence of a temporal relationship to the onset of the disease. Again, data from the literature are inadequate.

GENERAL SYMPTOMATOLOGY

Attempts to establish the exact time of onset are, of necessity, arbitrary in a disease of such diverse symptomatology and erratic course. However, certain symptoms apparently are consistent findings at the onset of this disease. In Group A, arthralgia or arthritis was present in 48 per cent, 25 per cent had fever, 18 per cent malaise, 14 per cent a skin rash (typical or atypical of LED), 14 per cent definite weight loss, 11 per cent Raynaud's phenomenon and 9 per cent edema (orbital or peripheral). Data concerning presenting symptoms were not available from Group B.

As the clinical picture of LED is subject to wide variation, it is most feasible to consider the appearance of the signs and symptoms of this disease in terms of the total course, rather than in terms of chronologic occurrence. Thus, in the absence of a typical skin lesion in the past or, today, a positive LE preparation, the disease remains difficult to diagnose early.

At some time in the course of the disease, fever was apparent in 95 per cent of Group A and in 99 per cent of 216 patients of Group B. In Group A, malaise and weight loss were present in all patients at some time during their course, but no exact figures can be given for the total incidence in Group B.

A skin rash was seen in the course of the disease in 68 per cent of Group

A and in 84 per cent of 323 patients in Group B. The rash was pruritic in 16 per cent of the patients in Group A, in keeping with the experience of others.⁴⁷ A typical butterfly rash was noted in 43 per cent (Group A); in half of these, it was a preterminal manifestation. In both Group A and Group B, and in agreement with Moore,²⁴ the rash varied in nature from mild erythema to vesicular and bullous lesions, which sometimes went on to erosion, crusting and scar formation. Alopecia, although reported occasionally,^{11, 48, 49, 50} was not a prominent feature (7 per cent of Group A). Ulcers of the oral mucosa were relatively frequent (18 per cent of Group A), and mucous membrane ulceration was noted in 15 per cent of 193 patients of Group B.

Arthritis or arthralgia was common and was noted in 77 per cent of Group A and in 76 per cent of 302 patients in Group B. Permanent clinical or x-ray evidence of joint involvement was present in only 34 per cent of Group A.

Cardiac manifestations were seen frequently in both groups (70 per cent of Group A, 68 per cent of Group B). Enlargement was present in 34 per cent of Group A and 15 per cent of 214 patients in Group B; murmurs were heard in 55 per cent of Group A (mitral diastolic, 9 per cent; mitral systolic, 36 per cent; basal systolic, 18 per cent), and in 24 per cent of the 214 patients reviewed in Group B; pericardial effusions were found in 16 per cent of Group A but in only one patient was a friction rub heard, while in 214 patients of Group B a pericardial effusion was noted in only 8 per cent. However, pericarditis as recognized clinically by electrocardiogram or by x-ray was reported in 23 per cent of Group A and in 21 per cent of the 214 patients in Group B. Hypertension of more than 150 systolic or 90 diastolic was noted infrequently in Group A, appearing in less than 18 per cent (transient in two and fixed in three patients), and elevation of blood pressure was said to be present in only 9 per cent of 214 patients in Group B.

In Group A, respiratory tract involvement was less frequently observed, being manifested by pleural effusion in 39 per cent, pleural rub in 20 per cent and pneumonitis in 20 per cent. Transient chest pain was a prominent complaint, though less frequently accompanied by objective findings. In Group B, there were symptoms or signs referable to the respiratory tract in 38 per cent, including a pleural effusion in 29 per cent of 216 patients.

Generalized glandular enlargement was noted repeatedly in 37 per cent of Group A and was present in 32 per cent of 216 patients in Group B.

In 36 per cent of Group A, gastrointestinal complaints were prominent, and 168 patients of Group B could be reviewed for this; 22 per cent of Group A and 17 per cent of Group B had abdominal pain; 18 per cent of Group A and 13 per cent of Group B exhibited nausea, vomiting and diarrhea, but in no instance was frank peritonitis observed. Hepatomegaly was found in 29 per cent of Group A and 12 per cent of Group B, and splenomegaly in 27 per cent of Group A and 17 per cent of 168 patients in Group B. The oc-

currence of these findings was rarely coincidental (six patients in Group A).

Peripheral and facial edema were present more frequently in Group A (25 and 12 per cent, respectively) than in 168 patients of Group B (13 and 8 per cent).

Raynaud's phenomena were observed in 16 per cent of Group A, while the incidence of these changes in the total series of 168 was low (8 per cent).

Eyeground changes were infrequently noted in Group B but occurred in 20 per cent of Group A (six patients with cotton-wool exudates, five with flame shaped hemorrhages, one with retinal edema, one with vasculitis with irregular beading, and one with punctate corneal erosion). The ocular manifestations of LED have recently been reviewed by Hollenhorst and Henderson,⁵¹ and include primarily the retinal lesions of superficial exudates, hemorrhage, papilledema, embolic petechiae, perivasculitis and arterial occlusion.

Neurologic or psychiatric manifestations were apparent in 18 per cent of Group A, 9 per cent developing disorientation and 7 per cent convulsions terminally. In one instance each, hemiparesis and schizophrenia were noted. Neurologic manifestations in LED have been reviewed by Sedgwick⁵² and Glaser.⁵³ In 216 patients of Group B, convulsions were present in 9 per cent, toxic psychosis in 5 per cent and hemiplegias in 2 per cent. Neuritis, focal central nervous system lesions, cerebral hemorrhage and chorea were seen in isolated instances.

LABORATORY FINDINGS

The laboratory findings play an important part in the diagnosis of LED and are, therefore, presented here in some detail; their incidence in Groups A and B is summarized in table 3.

Anemia was common and was frequently apparent at the onset in Group A, where the hemoglobin was less than 12 gm. in 95 per cent and the red blood cell count less than 4,000,000 in 68 per cent. The data reviewed in all patients of Group B revealed a hemoglobin of less than 12 gm. in 80 per cent at some time during the disease course. This figure should probably be higher, since complete follow-up laboratory data were not always available. A leukopenia was seen on the initial count in 47 per cent of Group A and in 70 per cent at some time during the disease course. Leukopenia of less than 5,000 during the course of the illness was noted in 68 per cent of Group B. A leukocytosis with a shift to the left was present during the course of the illness in 31 per cent of Group A and was incident to secondary infection in most instances. Although complete data were not available in either group to evaluate the total incidence of thrombocytopenia, purpura or thrombocytopenia was noted in approximately 10 per cent of 175 patients of Group B. The onset of LED as thrombocytopenic purpura has been noted.¹¹ In a recent review of the hematologic data on 111 patients with

LED, Michael et. al.⁵⁴ reported a high frequency of anemia (92 per cent), leukopenia (60 per cent), and thrombocytopenia (51 per cent), and included mention of three patients with severe hemolytic anemia. This last finding was reemphasized by Dubois,⁵⁵ who found three instances of hemolytic anemia with a positive Coombs' test in which LED developed subsequently. Repeated transfusion reactions were noted in two patients of Group A, but studies for hemagglutinins were not undertaken.

The elevation of the erythrocyte sedimentation rate to more than 50 mm. in the first hour (Westergren) was present in 86 per cent of Group A, and was recorded as elevated in 89 per cent of 245 patients in Group B. This latter finding may again be a reflection of limited laboratory data.

TABLE III
Laboratory Findings

	Group A* (per cent)	Group B† (per cent) (no. of pts.)
Hemoglobin < 12 gm.	95	80
Red Blood Cells < 4,000,000	68	—
White Blood Cells < 5,000	70	68
White Blood Cells > 10,000	31	—
Thrombocytopenia	—	10 (175)
Elevated Erythrocyte Sedimentation Rate	86	89 (245)
Albumin < 3.5 gm. %	57	—
< 3.0 gm. %	30	—
Globulin > 3.0 gm. %	82	42 (167)
Positive Cephalin Flocculation	77	—
Positive Hemolytic Streptococcus Agglutination	19 (26)	—
Positive Serologic Reaction for Syphilis	—	18
Kline	28 (40)	—
Wassermann—positive	15 (20)	—
anticomplementary	20 (20)	—
Albuminuria > 1+	70	58
Abnormal Urine Sediment	64	56
BUN > 20 mg. %	—	—
or	16	16 (216)
NPN > 50 mg. %	—	—
Electrocardiographic Changes	75	21 (119)

* Group A includes 44 patients.

† Group B includes 323 patients. If fewer could be used, total number in parentheses after percentage.

In Group A, a serum globulin value of greater than 3 gm. per cent was found in 82 per cent. In 167 patients of Group B, the serum globulin was increased over 3 gm. per cent in 42 per cent. A positive cephalin flocculation in 77 per cent of Group A was recorded. While the positive cephalin flocculation was usually associated with a high globulin, this correlation was not absolute, and instances of normal globulin associated with positive cephalin flocculation and of a high globulin with normal cephalin flocculation were seen. The serum albumin was less than 3 gm. per cent in 30 per cent and less than 3.5 gm. per cent in 57 per cent of Group A.

A hemolytic streptococcal agglutination test⁵⁶ was performed in 26 patients with joint manifestations in Group A, and in 19 per cent the result

was positive and in 11 per cent doubtful. This was found to have no prognostic significance.

Serologic tests for syphilis were performed: of 40 Group A patients tested with the Kline, 28 per cent were positive; in 20 patients in whom the Wassermann reaction was determined, it proved to be positive in 15 per cent and anticomplementary in 20 per cent. Positive serologic tests for syphilis were noted in 18 per cent of all patients in Group B. This figure is somewhat lower than the reports of Rein⁵⁷ and Montgomery and Mac-Creight,⁸ in which approximately 30 to 35 per cent of almost 300 sera from patients with LED had positive serologic tests for syphilis.

Albuminuria of greater than 1 plus was seen in 70 per cent of Group A and in 58 per cent of Group B. Red cells and numerous white cells and/or casts were observed in the urinary sediment at some time during the course of the disease in 64 per cent of Group A and 56 per cent of Group B. The presence of albuminuria and abnormal sediment was not correlated absolutely. Sixteen per cent of Group A patients showed nitrogen retention (blood urea nitrogen greater than 20 mg. per cent, or nonprotein nitrogen greater than 50 mg. per cent). Of these patients, all had urinary microscopic evidence of renal damage but only two had low specific gravities. The incidence of azotemia was low in 216 patients of Group B. An elevated blood urea nitrogen or nonprotein nitrogen was seen during the course of the disease in only 16 per cent; in an additional 4 per cent there was a terminal elevation.

In only one patient of our series was there laboratory evidence of jaundice, with serum bilirubin elevation of 6.5 mg. per cent. This occurred after repeated transfusion reactions and was correlated at post mortem with histologic evidence of central necrosis of the hepatic lobules and deposition of an eosinophilic amorphous material in these areas.

Roentgenograms of the chest in Group A were related directly to the clinical presence of a pleural involvement, effusion, pneumonitis or pericardial effusion, as described previously during consideration of the clinical course. Only rarely were joint x-rays useful in establishing the presence of permanent joint involvement.

Electrocardiograms showed changes in 75 per cent of Group A. In general, the alterations were indicative of myocardial or pericardial disease and included, as adequately described elsewhere,^{6,58} low voltage, inverted T waves, S-T wave changes, right and left axis deviation, tachycardia, or prolongation of the P-R interval. In 119 patients of Group B, electrocardiographic abnormalities were noted in 21 per cent and were substantially of the character previously noted.

DIFFERENTIAL DIAGNOSIS

Some insight into the semantic difficulties of LED diagnosis is offered by a consideration of the frequency with which other so-called collagen diseases were suggested as a diagnostic possibility. These can be enumerated

as follows in Group A: rheumatic fever, 11; rheumatoid arthritis, eight; mesenchymal disease, three; dermatomyositis, two; scleroderma, two; periarteritis nodosa, malignant arteritis and erythema nodosum, one each. Other diagnoses suggested included tuberculosis, sarcoid, lymphoma, Hodgkin's, chronic nephritis, glomerulonephritis, porphyria, Stevens-Johnson disease, syphilis, beriberi and undulant fever. Haserick,¹⁸ in a recent discussion of the plasma LE test, emphasizes the difficulty of clinical diagnosis. He noted that in 23 patients with a positive LE preparation, the diagnosis of rheumatoid arthritis in 11, rheumatic fever in three, and acute glomerulonephritis and chronic glomerulonephritis in one each, had been made prior to performance of the LE test.

AUTOPSY FINDINGS

Histopathologic criteria employed by Klemperer⁵⁹ for diagnosis of LED include the presence of fibrinoid change, metachromasia of ground substance, and infiltration of polymorphonuclear leukocytes and lymphocytes into connective tissue. Verrucous endocarditis was present in 55 per cent of his cases, pericardial lesions in 70 per cent, myocardial lesions in 35 per cent, "wire loop" change in the kidney in 60 per cent, focal loop glomerular necrosis in 85 per cent, and "onion skin" lesions in the spleen in 95 per cent.

In the 17 cases of Group A which came to autopsy, 15 postmortem examinations were performed at this hospital and total protocols of these autopsies are available. One of the two postmortem examinations done elsewhere confirmed the diagnosis of LED, while the other reported only old rheumatic heart disease with carditis and valvulitis. In the series of 15 patients, pericardial lesions were noted in seven instances, myocardial lesions in eight, verrucous endocarditis in five, "onion skin" lesions of the spleen in 11, and focal hepatic necrosis in four. Renal abnormalities were observed in 13 patients, in seven of whom "wire-looping" of glomerular capillaries was the outstanding lesion; in two, renal infarcts were noted. Generalized vasculitis was prominent in eight patients, pleuritis in 10, peritonitis in four. In one patient, evidence of both LED and dermatomyositis was apparent at autopsy.

One patient had a terminal septicemia, one a superimposed acute bacterial endocarditis, and another had leptomeningitis. Lobar or bronchial pneumonia was a frequent secondary finding at post mortem. While pneumonia or other secondary infection was a contributory lethal factor, the basic cause of death remained obscure in many instances.

No consideration of the pathology of this disease is complete without mention of the lack of specificity of the skin biopsy. In a large series of patients studied by Montgomery and MacCreight,⁸ less than one-fourth of the skin biopsies were positive as evidenced by alteration of collagen or fibrinoid change in superficial vessels. In fact, where these changes were noted, they were no more prominent than in many other chronic inflam-

matory infectious diseases of the skin. However, these authors believe that the diagnosis can be made by biopsy of an active untreated lesion of the skin on the basis of dilatation of the capillaries, and edema of the walls of the arterioles and venules.

Of 14 skin biopsies performed in Group A, one-half were compatible with LED, the remainder being reported as nonspecific inflammation. Of

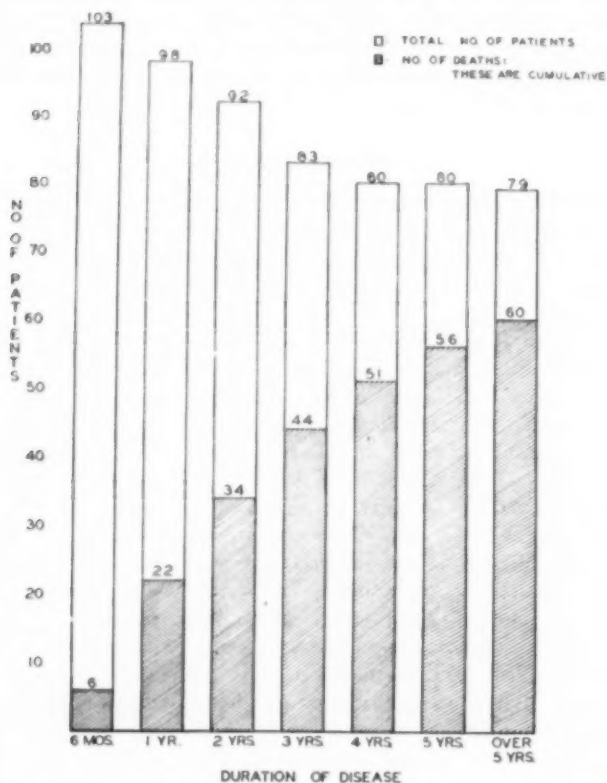


FIG. 1. Summary: number of deaths observed in a group of patients with lupus erythematosus disseminatus with varying duration of disease.

the 16 patients diagnosed LED at autopsy, nine had had skin biopsies, of which only three were positive.

DURATION AND COURSE OF THE DISEASE (FIGURE 1)

Of the 44 patients in Group A, 31 have died, with autopsies performed in 17 instances. In these 17 patients (16 with an autopsy diagnosis of LED, the duration of illness (table 4) from the onset of disease paralleled that of

Group B. Of the 14 cases in which no postmortem examination was made, a biopsy of skin or lymph node was found to be compatible with LED in three patients. The diagnosis in the remaining 11 patients who have died must rest upon the clinical diagnostic criteria referred to earlier. Of the 13 patients who were alive when last seen, five have been lost to follow-up. Even if these five were presumed dead, the follow-up periods would be relatively long, since the history of the duration of disease was over two years in one and over three years in another. Another of these patients had a five year history of the disease and, at last report, had evidence only of hypertension. One of the two remaining patients in this group was observed over a period of eight years and was practically asymptomatic on her last visit. The other patient lost to follow-up was in remission when last seen after a period of observation of six years, but was subsequently reported in exacerbation at another hospital.

Of the patients definitely known to be alive, one has a four year follow-up, has had three normal pregnancies during this interval, and has remained asymptomatic. Another such patient, who gives a history of 14 years of

TABLE IV
Duration of Disease at Time of Death in 16 Patients (of Group A) with an Autopsy Diagnosis of Lupus Erythematosus Disseminatus

Duration	No. of Patients
Up to 6 months	2
1 year	5
2 years	3
3 years	2
4 years	1
Over 5 years	3

disease, has undergone two pregnancies without ill effect. One patient is now working after 14 years of disease, although malaise continues to be a problem. Another patient, 10 years after the onset of her illness, has been diagnosed as allergic eczema at another hospital. Three other patients are alive after a follow-up of 13 years; one has only Raynaud's phenomena, and another has occasional intermittent joint pains and some objective evidence of rheumatoid arthritis, and has been recently demonstrated to have a positive LE cell test. The last patient, after 20 years of illness, is now hospitalized with far advanced rheumatoid arthritis.

Thus, in Group A, 13 patients (30 per cent) were alive at a period of greater than five years. While it is possible that the diagnosis of LED in the above group of patients may have been faulty, it must be emphasized that all the cases included here fulfill most of the diagnostic criteria.

Examination of the duration of illness in the cases under consideration is important, since this may suggest at least a statistical basis for prognosis. To the group reviewed above, we have added 59 case reports from the literature which included information permitting an estimate of the duration of the illness from the date of onset. The importance of the observation that 22 per cent of 103 patients in this Group B were alive at greater than five

years is self-evident. Four of these patients subsequently died; three were lost to follow-up. The remaining 16 cases include one patient alive at 20 years, two at 14 and three at 13 years after onset of the disease.

Of the 60 patients of the series (Group B) who had died, six were dead within six months of the onset of the illness, an additional 16 within one year, 12 more within two years, another 10 within three years, seven others within four years, and five within five years. In Group B, 6 per cent of patients observed for six months had died; 22 per cent of those observed for one year; 37 per cent of those for two years; 55 per cent of those for three years, 64 per cent for four years and 70 per cent for five years.

Of the living patients in Group B who had been followed for less than five years, five had had their illness for less than six months, six others for less than one year, nine for less than two years, three for less than three years, and one for less than five years. An additional 19 were alive after being followed for more than five years.

While it is obvious from the consideration of the mortality figures that the prognosis in LED is unfavorable, it is likewise apparent that in some 20 per cent a duration of illness of greater than five years may be expected. In Group A there are at least six of the 44 patients who are relatively asymptomatic for periods ranging from four to 20 years.

DISCUSSION

It has been noted already that in any given group of patients, approximately 20 per cent will be alive at periods of greater than five years from the onset of the disease. This fact must be considered in an evaluation of a therapeutic regimen. Much has been said of the efficacy of the treatment of LED with corticotrophin and cortisone. In a recently reported series of patients, Dubois²⁰ has stated that, while the effect of the new hormones has been noteworthy in the treatment of LED, there is no evidence as yet that life expectancy is prolonged. Soffer and Bader²³ have also reported recently on the use of these agents in the treatment of LED. Examination of their data reveals that six of 18 patients treated by them with corticotrophin or cortisone for from three to 20 months had died by the time of the reporting. Again, it must be emphasized that the expected mortality of the disease without treatment approximates that seen with the more recent potent antiphlogistic substances. The usefulness of these agents in the palliative therapy of the patient with LED cannot be denied, but it will remain for further long-term follow-up to delineate the rôle of these hormones and of therapies yet to come in the modification of the life span of these patients.

SUMMARY

1. A study of the natural history of LED has been undertaken, based upon a group of 44 observed patients and upon an additional 279 patients reported in the literature.

2. The clinical and laboratory picture of this disease has been reviewed and the findings have been presented.

3. The prognosis of the disease in terms of its natural history has been evaluated. While the prognosis is unfavorable, 22 per cent of the patients remain alive for periods in excess of five years.

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THE "PARARHEUMATIC" ARTHROPATHIES *

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THE term "diffuse collagen diseases" was introduced by Klemperer and his co-workers¹ to identify a group of disorders characterized by morphologic changes in the connective tissues of the body. Although perhaps other diseases should also be included, rheumatic fever, rheumatoid arthritis, lupus erythematosus disseminatus, polyarteritis nodosa, diffuse scleroderma and dermatomyositis are currently recognized as members of this group.

In the voluminous literature on various aspects of the collagen diseases, scant attention has been paid to the rheumatic manifestations of diseases in this group other than rheumatic fever and rheumatoid arthritis. The purpose of this report is to review the pertinent literature and to present our own observations on the musculoarticular symptoms of lupus erythematosus disseminatus, polyarteritis nodosa, diffuse scleroderma and dermatomyositis.

Because of the widespread distribution of connective tissue in the body, morphologic alterations in this tissue may lead to lesions in such structures as the blood vessels, the viscera and the serous membranes. It is therefore inevitable that in all of these diseases one may encounter clinical evidence of vascular lesions, visceral involvement, pericarditis, pleuritis, dermatitis and arthritis. It is likewise apparent that, in some instances, the clinical manifestations of these diseases may closely simulate each other and even be indistinguishable, a feature referred to as "overlapping."² Fortunately, rheumatoid arthritis and rheumatic fever usually exhibit clearly defined and easily recognized clinical patterns. However, the group of other diseases in this category, disseminated lupus erythematosus, polyarteritis nodosa, diffuse scleroderma and dermatomyositis, are apt to present protean manifestations, bizarre clinical pictures, and difficult problems in differential diagnosis. Oftentimes, because of anomalous manifestations and "overlapping," one can only designate a disease as belonging to the latter group without being able specifically to identify it.

To segregate these two groups of diseases, the terms "rheumatic" † and "pararheumatic" ‡ have been applied to rheumatic fever and rheumatoid

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† Note: The term "pararheumatic" was introduced by Teilum (Acta med. Scandinav. 123: 126, 1946), who classified lupus erythematosus disseminatus, polyarteritis nodosa and "arteriolitis granulomatosa (allergica)" as "pararheumatic" diseases. By use of this terminology he implied a pathogenetic relationship between them and the "rheumatic" disease, rheumatic fever. He regarded the latter as an etiologically and clinically specific lesion.

arthritis on the one hand, and lupus erythematosus disseminatus, polyarteritis nodosa, diffuse scleroderma and dermatomyositis on the other. This differentiation is supported by the fact that the "pararheumatic" diseases have a more serious prognosis, and by the generally accepted opinion that, in some of these "pararheumatic" disorders, serious harm may be done by forms of treatment used in rheumatoid arthritis, such as ultraviolet irradiation, fever therapy and chrysotherapy.

With the collagen diseases separated into "rheumatic" and "pararheumatic" groups, a logical corollary is the identification of their arthropathies as "rheumatic" and "pararheumatic," respectively. The former term is superfluous, since rheumatic fever and rheumatoid arthritis are, as a rule, easily diagnosed. The term "pararheumatic" arthropathy, on the other hand, is useful in designating the musculoarticular manifestations of a disease which is as yet unidentified within the group. This is especially valid since these manifestations are of themselves not diagnostic. Once the correct diagnosis is established, the arthropathy is listed as a manifestation of the disease, e.g., arthropathy of lupus erythematosus disseminatus.

In our observations we have been impressed not only with the high incidence of musculoarticular manifestations in lupus erythematosus disseminatus, polyarteritis nodosa, diffuse scleroderma and dermatomyositis, but also with the frequency of these symptoms as the presenting complaints. The earliest possible recognition of the rheumatic-like and rheumatoid-like features of this group of diseases is important, therefore, for correct diagnosis, prognosis and treatment. It is with these aspects of the so-called "pararheumatic" diseases that we shall concern ourselves here.

ARTHROPATHY OF LUPUS ERYTHEMATOSUS DISSEMINATUS

Lupus erythematosus disseminatus is a systemic disease of unknown etiology, characterized by clinical symptoms of variable severity that precede, accompany or follow the appearance of the cutaneous eruption. The disease occurs preponderantly in females. Its outstanding features aside from the "butterfly" rash which is not invariably present, are hematuria and renal insufficiency, leukopenia, lymphadenopathy, fever, pleuritis, pericarditis and arthritis. The presence of the "L.E." phenomenon³ in the bone marrow or peripheral blood is considered diagnostic. The course varies over a period of weeks, months or years. Remissions and exacerbations are common. However, the ultimate prognosis is poor and recovery is unusual.

The "pararheumatic" diseases were considered to be of allergic origin but similar pathogenetically to rheumatic fever.

Although we have resurrected the terms "rheumatic" and "pararheumatic," we have employed them in a somewhat different sense. The term "rheumatic" applies to the two common "rheumatic" diseases, rheumatic fever and rheumatoid arthritis, rather than to the former alone; "pararheumatic" applies to the other diffuse collagen diseases. In the use of this terminology, we imply that although these two groups of diseases share morphologic alterations of the connective tissue, there are important clinical differences from the standpoint of diagnosis, prognosis and treatment. There are no other implications.

The average duration is about 18 months. The Libman-Sacks syndrome represents an atypical form of the disease (*lupus sine lupo*).

The occurrence of rheumatic manifestations in this disease has been noted by many observers. The exact incidence is difficult to ascertain. The most recent report of Tumulty and Harvey⁴ records the incidence of joint involvement as 85 per cent. The Reifenshteins⁵ reviewed 17 selected autopsied cases from the literature and added one of their own. Articular manifestations, including arthralgia and arthritis, were present in all. Of the 12 cases studied by Rose and Pillsbury,⁶ five presented "arthralgia." Five of the six autopsied cases reported by Guion and Adams⁷ had arthritis, which lasted six months to six and one-half years. Cluxton and Krause,⁸ in their review of the literature, stated that "arthralgia" is usually present at one time or another. "Migratory evanescent arthritis" occurred in 23 of 30 cases studied by Coburn and Moore.⁹ Baehr et al.¹⁰ noted arthritis in 17 of their 23 cases. In the most complete study of the rheumatic manifestations of the disease reported in the literature, Slocumb¹¹ found the incidence of joint involvement in the chronic disseminated, subacute disseminated and acute disseminated forms to be 20 per cent, 57 per cent and 63 per cent, respectively.

Most frequently, the rheumatic manifestations precede the appearance of the eruption, although they may accompany or follow it. Slocumb¹¹ reported that in eight of 10 patients joint symptoms preceded the skin lesions by periods of time varying from one and one-half months to five years. The onset in the series of four cases reported by Friedberg, Gross and Wallach¹² was marked by polyarthritis. In four of Guion and Adams's⁷ six cases, joint symptoms preceded the rash. In three of the four cases reported by Cluxton and Krause,⁸ the presenting complaints were arthritic.

The rheumatic manifestations of disseminated lupus erythematosus have been described by Slocumb.¹¹ Three of his 10 cases had fibrositic symptoms, which were of three months' to two years' duration. The complaints were usually recurrent pain, tenderness and stiffness affecting the muscles and joints. Initially the attacks were infrequent and of brief duration, and involved only one or two regions. Later they became more frequent, lasted longer and were widespread. As in true fibrositis, the stiffness and aching could be relieved somewhat by heat, exercise and salicylates.

In each of the 10 patients studied by Slocumb,¹¹ acutely painful, swollen joints with local redness and heat developed. The acute inflammation generally lasted one to two days, then disappeared completely, leaving only residual stiffness and aching. Salicylates partially or completely relieved the joint symptoms but had no effect on the fever.

Six patients in Slocumb's series¹¹ suffered acute and subacute attacks of swelling, pain and redness of the joints, with residual joint swelling, stiffness and pain between attacks. One patient developed a chronic, progressive, deforming arthritis.

Similar descriptions of the joint involvement in lupus erythematosus disseminatus are found in the cases reported by others. The articular mani-

festations can be classified into three major groups: first, myalgias and arthralgias; second, acute or subacute migratory polyarthritis; and third, chronic, progressive polyarthritis with deformity. Study of the reported cases falling into these categories reveals that they were often misdiagnosed as fibrositis, rheumatic fever and rheumatoid arthritis, respectively. The true nature of the disease finally became apparent either clinically or at necropsy.

Diagnostic difficulties are very prone to occur in cases of lupus erythematosus disseminatus showing clinical evidence of a rheumatoid-like arthropathy. Such cases are not unusual in the recorded literature,¹²⁻¹⁵ and in our own experience.

ARTHROPATHY OF POLYARTERITIS NODOSA

Polyarteritis nodosa is a systemic disease of unknown origin, although the work of Rich and Gregory¹⁶ suggests an allergic etiology. It is characterized by fever, polyneuritis and polymyositis, gastrointestinal, cardiac and renal lesions, cachexia and, frequently, leukocytosis, eosinophilia, arthritis and allergic phenomena. Cutaneous eruptions and palpable subcutaneous nodules may occur. The disease appears in both sexes but males are most frequently affected. The course generally is downward over a period of months or longer.

The presence of neuromuscular symptoms caused by the polymyositis and polyneuritis occurring in this disease is well known; the articular manifestations are less commonly appreciated. Muscles are affected clinically and pathologically in about 30 to 35 per cent of cases.^{17, 18} The predominant symptoms are pain, tenderness, muscle spasm and atrophy, and sensory disturbances. In Jones's cases,¹⁹ myalgia was noted in 64 per cent, arthritis in 57 per cent and nodules in 14 per cent. Objective signs of joint involvement were noted in only one patient, who showed fusiform swelling of some of the interphalangeal joints of the fingers. Four of the nine patients reported by Gelfand and Aronoff²⁰ exhibited osteoporosis. All of McCall and Pennock's seven cases²¹ complained of joint pains or myalgias; definite articular swelling was observed in but two. Harris et al.²² reviewed all of the 101 cases of this disease reported in the English literature up to 1939 and found the incidence of arthritis to be 27 per cent. Logue and Mullins²³ reviewed an additional 76 cases and found arthropathy in 34 per cent of the total of 177 cases.

Articular symptoms not infrequently constitute one of the earliest manifestations of the disease. In the series of 100 cases reported by Boyd,²⁴ complaints referable to the joints were the first symptom in 14, and the second in 11.

Review of the cases reported in the literature shows that the joint manifestations of polyarteritis nodosa, like those of lupus erythematosus disseminatus, can be classified into three major groups: first, myalgias and

arthralgias; second, acute and subacute polyarthritis; and third, chronic, progressive, deforming polyarthritis. Again, as in lupus erythematosus disseminatus, the articular manifestations of polyarteritis nodosa are frequently misdiagnosed as fibrositis, rheumatic fever and rheumatoid arthritis.

ARTHROPATHY OF DIFFUSE SCLERODERMA

Diffuse scleroderma is a systemic disease of unknown etiology, characterized by edema, induration, pigmentation and atrophy of the skin. Vasomotor disturbances, such as vasospasm and Raynaud's phenomenon, as well as arthritic symptoms are commonly noted. The gastrointestinal tract and heart are sometimes involved by the sclerodermatous process. Calcinosis circumscripta or universalis is a frequent accompaniment. Constitutional symptoms, such as fever, tachycardia or weight loss, are seldom seen. The disease occurs preponderantly in women. The course is ordinarily chronic and the prognosis is favorable in comparison with the other "pararheumatic" diseases.

Little information is available in the literature on the arthritic manifestations of this disease. Osler²⁶ reported in detail eight cases of scleroderma; in five of these there were symptoms of an arthritic nature, which varied from generalized recurrent arthritis to swelling and stiffness of the hands. The most complete studies are those of O'Leary and Nornland²⁶ and O'Leary and Waisman.²⁷

In 28 of 48 cases of generalized scleroderma, O'Leary and Nornland²⁶ stated that arthritic symptoms were the initial evidence of the disease. The extent and severity of the joint signs were variable. Some patients presented only slight pain, swelling and stiffness of the hands, followed by hardening of the skin. In other cases there was generalized severe musculoskeletal pain, with swelling and stiffness of the joints. According to the authors, the symptoms, except for the scleroderma, simulated a severe generalized arthritis.

Of the 28 cases in which symptoms of arthritis were present, the hands were initially involved in 12. Many of these subsequently developed generalized joint pains. In seven patients all of the extremities were involved from the beginning, while in three the condition began in other joints. In six cases there were generalized pain and stiffness of the joints, weight loss and systemic symptoms. Owing to the predominant articular features, roentgenograms of the hands were taken in 16 cases of scleroderma and sclerodactylia. In six of these the films were negative; in four of the 10 remaining cases, marked "periarticular arthritis" was noted. One showed less marked arthritic changes. Two patients showed destructive changes in the bones of the hands. In three cases there was loss of the distal phalanges. Sclerodactylia was observed in all but five of the cases of generalized scleroderma.

O'Leary and Waisman²⁷ described the findings in 64 patients with acro-

sclerosis, which they distinguish from diffuse scleroderma. According to them, acrosclerosis is a syndrome combining Raynaud's phenomenon with scleroderma of the distal part of the extremities, the face, neck and upper part of the chest. One-fourth of the patients with acrosclerosis reported symptoms in the large joints (elbows, shoulders, knees and ankles). In several, these symptoms preceded the vasomotor signs. The complaints were mainly those of stiffness, aching and swelling of the affected joints. The authors thought that the pathologic process was probably localized to the periarticular tissues and that it was usually independent of the scleroderma of the overlying skin. The hands showed the typical, tense, smooth skin of the disease. Clubbing of the nails, shortening of the terminal phalanges, scars over the proximal interphalangeal joints, puffiness, stiffness of the fingers, coolness and moistness of the skin, and a pale pink or cyanotic color were other significant features observed in the hands.

Most patients with scleroderma are treated for months or years for one of the rheumatic diseases before the true nature of their condition is recognized.

ARTHROPATHY OF DERMATOMYOSITIS

Dermatomyositis is a nonsuppurative, inflammatory disease of the skin, subcutaneous tissue and skeletal muscles. The affected muscles are painful, tender, weak and atrophic. The skin lesions are nonspecific and pleomorphic. Other features are fever, weight loss, edema, localized or systemic calcification, leukocytosis, eosinophilia and slight anemia. The disease may occur at any age but those between 10 and 50 years of age are most often affected. The course is variable, with a mortality rate of from 50 to 60 per cent.

In this disease, "rheumatic" manifestations are common and consist preponderantly of muscular symptoms. In the nine cases reported by Jager and Grossman,²⁸ muscle involvement was constant. Every patient complained of muscular stiffness, which was worse on arising and was usually relieved by gentle exercise. It was aggravated, however, by severe or prolonged exertion. Three patients complained of muscular cramps, which tended to be more severe at night. Palpation of the muscles, particularly those of the shoulder girdle, revealed tenderness in every case but one. In six patients muscle atrophy was demonstrable. Most often the musculature of the shoulders and pelvic girdles was affected. Three patients had arthritic pains without swelling of the joints. O'Leary and Waisman²⁹ recorded articular symptoms in six of 40 cases. In two, arthritis was present; in the others, transient arthralgias occurred at the onset of the illness.

Keil's³⁰ views on this subject are as follows: "Dermatomyositis generally spares the joints. There are, however, patients who complain of pains that seem to be about or near the articulations, but it is likely that in such instances, the deeper tendons, the terminal portions of the muscles, or even the subcutaneous tissues in this general region, will be found to be implicated

by a vascular, inflammatory or edematous process. While there is no clinical evidence of genuine involvement of joints in dermatomyositis, there are encountered on the other hand, articular deformities due to contractures produced by fibrosis of the parts already mentioned. The contractures are generally observed in well established cases, but occasionally they may occur surprisingly early in the course. In the end stages, the clinical picture of myositis fibrosa is produced. In cases of dermatomyositis, such contractures are observed chiefly about the elbows, knees, hips and fingers. In occasional instances of dermatomyositis, there may be rarefaction of the bones in the neighborhood of the joints as shown by roentgenograms; the precise genesis of this condition is unclear at present."

A possible relationship between Weber-Christian disease, nodular non-suppurative panniculitis and dermatomyositis has been described.³¹ Weber-Christian disease may be associated with joint pains and arthritis. Within the nodules seen in Weber-Christian disease, vascular changes have been described which strongly resemble those seen in the "pararheumatic" diseases.

ARTHROPATHY OF DISSEMINATED ARTERITIS

Progressive disseminated arteritis of unknown origin has been described.^{32, 33} Although it bears certain resemblances to lupus erythematosus disseminatus and polyarteritis nodosa, there are important differences. The clinical features include vascular lesions, occlusion of arteries, gangrene of digits and patches of skin, fever, purpura and widespread visceral involvement. Articular manifestations have not been reported thus far in this group.

Among our own cases, as will be noted later in this presentation, there have been several instances of arthropathy in which muscle biopsy has revealed the presence of a disseminated "arteritis" of unknown type. Although it is most likely that, at some future time, it will be possible to place these patients in one of the known disease categories, such as polyarteritis nodosa, lupus erythematosus disseminatus, etc., it is conceivable that some may belong to the group discussed.

STUDY OF MATERIAL

From a clinical standpoint, we have found it convenient to group patients with suspected or proved "pararheumatic" arthropathy into one of four groups: (1) possible "pararheumatic" arthropathy; (2) probable "pararheumatic" arthropathy; (3) definite "pararheumatic" arthropathy, type unknown, and (4) definite "pararheumatic" arthropathy, type known. These distinctions permit the use of a general diagnostic term which removes the patient from conventional rheumatic categories.

Cases of possible "pararheumatic" arthropathy are those in whom the musculoarticular and clinical manifestations are sufficiently atypical of known

rheumatic diseases to warrant consideration of the diagnosis. Cases of probable "pararheumatic" arthropathy are those in whom arthropathy is either typical or atypical of known rheumatic disease, but in whom the weight of clinical evidence makes the diagnosis of "pararheumatic" disease probable. The diagnosis of definite "pararheumatic" arthropathy is made only in the presence of indisputable and/or pathologic evidence of a "pararheumatic" disease. When a specific diagnosis can be made, the arthropathy is listed as a manifestation of the disease in question. When the exact diagnosis is not known, the condition is classified as definite "pararheumatic" arthropathy, type unknown.

During the years 1938 to 1947, inclusive, there were admitted to the Medical Services of Bellevue Hospital a total of 13 proved cases and one possible case of lupus erythematosus disseminatus. During the same period, there were also eight cases of proved, one case of probable and three cases of possible polyarteritis nodosa. The diagnosis of dermatomyositis was probable in another case, and that of diffuse scleroderma, definite in still another. There were five cases of definite "pararheumatic" arthropathy of unknown type and three possible cases belonging in this category. The total number of cases of suspected or proved "pararheumatic" arthropathy was 36.

Of the 13 cases of proved lupus erythematosus disseminatus, five patients suffered from myalgias and arthralgias; three patients, from an acute or subacute polyarthritis, and five from a chronic progressive polyarthritis with deformity. In five of the 13 cases, the articular manifestations preceded the appearance of the diagnostic cutaneous eruption. The patient with possible lupus erythematosus disseminatus presented fibrositic symptoms.

Of the eight cases of polyarteritis nodosa, seven had joint symptoms. Arthralgias and myalgias were noted in six instances, acute polyarthritis in two and a chronic, deforming polyarthritis in one. (More than one type was noted in the same patient.) In three of the eight cases, the first symptoms of polyarteritis nodosa were "rheumatic." The presenting symptoms of the case of probable polyarteritis nodosa were those of a chronic arthritis resembling rheumatoid arthritis. Of the three possible cases of periarteritis nodosa, one had fibrositic symptoms.

The case of probable dermatomyositis presented complaints of a fibrositic nature. In the patient with diffuse scleroderma, the earliest symptoms were those of joint pain and swelling.

The initial complaints and predominant clinical features were musculo-articular in all the cases of proved and possible "pararheumatic" arthropathy. Of the five proved cases, all had myalgias and arthralgias. In three, a rheumatoid-like arthropathy developed. One had cystic tendonitis, and one, a fibrositis-like clinical picture. Of the three possible cases, one had chronic deforming polyarthritis, one had myalgias and arthralgias, and one, bizarre articular manifestations.

CASE REPORTS

The following case reports illustrate some of the clinical and diagnostic problems encountered by us in the "pararheumatic" arthropathies.

Case 1. Possible "pararheumatic" arthropathy, type unknown. Rheumatoid-like arthropathy. A 42 year old white female was admitted to the Fourth Medical Division, Bellevue Hospital, on August 8, 1944, with chief complaints of joint pains, abdominal pain and weight loss of seven months' duration.

The patient had been well until seven months before admission, when she was treated at another hospital for "double pneumonia." Following discharge from this hospital, she noted simultaneously the gradual onset of crampy abdominal pain, painful swelling of multiple joints, anorexia and weight loss.

Examination on admission was negative except for emaciation and the articular findings. There was fusiform swelling of the proximal interphalangeal joints of the fingers of both hands, with pain, tenderness and stiffness. Most of the other joints were painful and stiff, but there was no swelling or deformity.

While in the hospital the patient's course was steadily downward. She ran an irregular fever, the temperature varying between 99° and 104° F. except for the last 12 days of her illness, when she was afebrile. Death occurred two months after admission. Autopsy permission was not obtained.

Laboratory data were essentially negative except for a moderate secondary anemia. The sedimentation rate was 10 mm./hr. (Westergren). Urinalysis was negative. Roentgen studies of the hands were reported as showing "advanced atrophic arthritic changes of the interphalangeal joints with marked narrowing of the joint spaces." A chest film and barium enema were negative.

The clinical diagnosis was that of an unusually severe, fulminating rheumatoid arthritis.

Comment: In retrospect, the rather fulminant nature of this illness with rapidly fatal termination, in association with a rheumatoid-like arthropathy, even to characteristic radiographic findings, suggests that this patient falls into the category of the "pararheumatic" arthropathies. Unfortunately, autopsy or biopsy confirmation of such a diagnosis was lacking. It is extremely unusual for rheumatoid arthritis to follow such a course.

Case 2. Definite "pararheumatic" arthropathy, type unknown. Possible polyarteritis nodosa. Fibrositis-like picture. A 52 year old white female was admitted to the Third Medical Division, Bellevue Hospital, on September 7, 1939, with complaints of pain and stiffness of the neck of one month's duration.

One month prior to entry the patient had developed a painful, stiff neck and bilateral occipital headache. These symptoms were more or less constant until admission.

Inquiry revealed that she had had vague pains in her arms and calf muscles in the preceding few months. Two years previously she had been told she had hypertension. The remainder of the past history was noncontributory.

Examination revealed a moderately obese white woman in no acute distress. The left side of the neck and the occiput were tender on palpation. The apical impulse of the heart was in the fifth interspace at the midclavicular line. The heart sounds were of good quality. A soft systolic murmur was heard at the apex but was not transmitted. The blood pressure was 142/78 mm. of Hg. The remainder of the examination was negative.

While in the hospital the patient ran a low grade fever, varying between 100° and 102° F., for nine weeks. The headache and stiff neck disappeared completely in one week, but the myalgias and arthralgias persisted. On the eighteenth hospital day she developed signs of an acute bronchitis, which subsided one week later.

Repeated urinalyses were essentially negative. The sedimentation rate was 64 mm./hr. (Westergren). The white cell count ranged between 11,800 and 18,750, with a marked shift to the left. Eosinophilia up to 12 per cent was noted on various occasions. Repeated blood cultures were negative. Stool cultures and blood agglutinations were negative. Skin tests with trichinella antigen were negative. X-ray examination of the skull, cervical spine and chest disclosed no abnormalities. Intravenous pyelography was negative. An electrocardiogram showed left axis deviation but was otherwise within normal limits.

A muscle biopsy was performed during the patient's stay in the hospital because of the persistent fever, eosinophilia and myositic complaints. Histologic examination revealed the presence of "many small arteries showing thickening of the media and infiltration of the media and adventitia with lymphocytes and small cells whose cytoplasm was scanty and whose nuclei were small." The findings were interpreted by the pathologist as being consistent with polyarteritis nodosa.

The patient was discharged on November 22, 1939, completely asymptomatic. No follow-up studies are available.

Comment: This patient presented essentially a fibrositis-like clinical picture. However, the presence of persistent fever, especially in connection with eosinophilia, suggested the possibility of one of the "pararheumatic" diseases. While not conclusive, the findings of the muscle biopsy, taken together with the clinical findings, justify the diagnosis of possible polyarteritis nodosa.



FIG. 1. (Case 3) Possible polyarteritis nodosa. Rheumatoid-like arthropathy. Limitation of motion of the fingers of both hands.

Case 3. Definite "pararheumatic" arthropathy, type unknown. Possible polyarteritis nodosa. Rheumatoid-like arthropathy. A 54 year old white male was admitted to the Fourth Medical Division, Bellevue Hospital, on November 7, 1945, with complaints of painful, swollen joints, anorexia and weight loss of six months' duration.

Six months prior to admission the patient had noted pain and swelling of his left great toe. Thereafter, and almost continuously up to the time of admission, he had painful, migratory swelling involving the knees, ankles, elbows, wrists and the finger joints. The joints were tender, painful, red and swollen. Persistent stiffness and limitation of motion developed in the elbows and fingers. By the time of admission there had been a weight loss of 40 pounds.

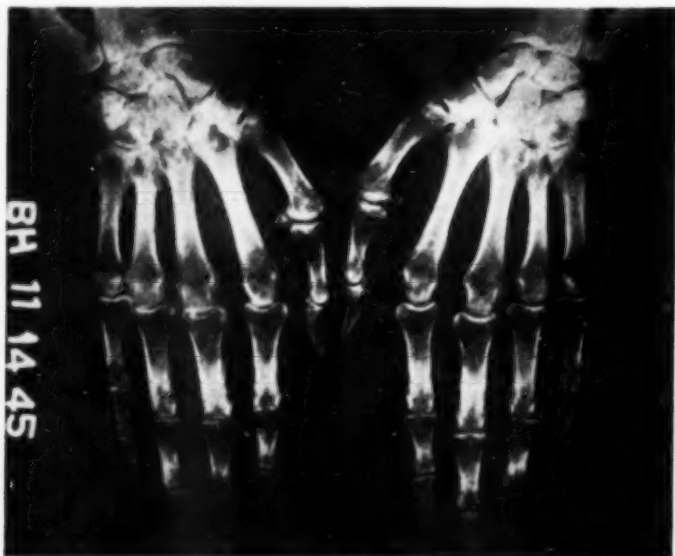


FIG. 2. (Case 3) Possible polyarteritis nodosa. X-rays of the hands showing osteoporosis, more marked at the articular ends of the bones, and narrowing of the proximal interphalangeal joints. Findings indistinguishable from those occurring in rheumatoid arthritis.

Examination disclosed a chronically ill patient who showed evidence of considerable weight loss. The blood pressure was 152/98 mm. of Hg. Both shoulders showed limitation of motion but were otherwise normal. There were definite thickening and tenderness of the proximal interphalangeal joints of the fingers of both hands, with limited motion at these joints (figure 1). There was likewise suggestive ulnar deviation of the hands. The remainder of the examination was essentially negative.

Repeated urinalysis showed a trace to 1 plus albumin, with 2 to 10 white cells per high power field. Examination of the urine for Bence-Jones protein was negative. The red cell count was 3,380,000 and the hemoglobin 10 gm. The white cell count was 9,450, with 63 per cent neutrophils, 10 per cent transitional cells and 27 per cent lymphocytes. The blood Wassermann was negative. The sedimentation

rate ranged between 32 and 37 mm./hr. (Westergren). The blood uric acid on two occasions was 4.2 mg. per cent and 3.0 mg. per cent. The trichinosis precipitin test was positive in a titer of 1:1,280, but the complement fixation test for trichinosis was negative. The non-protein nitrogen was 30 mg. per cent. The total proteins were 5.4 gm. per 100 c.c., with an A/G ratio of 1. An x-ray of both hands (figure 2) showed diffuse osteoporosis and narrowing of the proximal interphalangeal joints.

The clinical diagnosis was rheumatoid arthritis. Because of the marked asthenia and cachexia, a muscle biopsy was suggested. The pathologic diagnosis was "arteritis with organization and canalization; possible polyarteritis nodosa."

The patient was treated symptomatically with salicylates, a nutritious diet and physiotherapy. He gradually improved and was discharged on January 29, 1946. He was followed in the out-patient clinic. It was noted that his joint difficulties gradually subsided. He regained his weight and strength. From time to time he complained of left-sided chest pain, but nothing was ever found on clinical, electrocardiographic or roentgenologic examination to explain it.

Comment: This patient was admitted to the hospital with findings which could be considered more or less typical of rheumatoid arthritis. The diagnosis of one of the "pararheumatic" diseases was suggested by asthenia and cachexia out of proportion to the degree of joint disability. A muscle biopsy confirmed this possibility and suggested the diagnosis of polyarteritis nodosa. In spite of the prolonged and favorable course, this diagnosis seems justified. Cases with longer duration and even with recovery have been reported in the literature.

Case 4. Definite "pararheumatic" arthropathy, type unknown. Rheumatoid-like arthropathy. A 64 year old white female was admitted to the Fourth Medical Division, Bellevue Hospital, on June 17, 1947, complaining of multiple joint pains and swelling of seven months' duration.

Seven months prior to admission, without antecedent trauma, infection or emotional crisis, the patient had a sudden onset of severe pain and swelling of her ankle joints. The joints were hot, red, tender and stiff. In the next month she developed a migratory polyarthritis involving the wrists, fingers, knees, elbows, shoulders and feet. At the time of admission the finger joints were most severely affected. There was a weight loss of 15 pounds.

Examination disclosed an emaciated, middle-aged woman who appeared chronically ill. Positive physical findings were limited to the musculoskeletal system. There were marked spindling, pronounced erythema, slightly increased local heat and beginning flexion contractures of the proximal interphalangeal joints of the second to fifth fingers of both hands. The distal interphalangeal joints showed slight hyperextension but were otherwise not remarkable. There was marked weakness of the hands but there was no ulnar deviation. The wrists showed slight tenderness and swelling, but no redness or increased local heat. There was slight limitation of motion of the elbows, which were tender but otherwise not remarkable. Both shoulders were tender and motion was slightly limited. The right knee was swollen and warm, and contained a small amount of fluid. The left knee was tender but not swollen. Both ankles were swollen, warm and tender to palpation.

Laboratory data were as follows: Repeated urinalyses were negative except for an occasional trace of albumin. Impairment of renal function was evidenced by a maximal concentration of 1.015 and a phenolsulfonphthalein excretion of less than 20 per cent in two hours. The red cell counts ranged between 3,550,000 and 3,970,000. The hemoglobin was 10 to 10.6 gm. The sedimentation rate ranged between 102 and 126 mm./hr. (Westergren). The white cell counts ranged between 6,150 and 12,500,

with a slight increase in neutrophils (73 to 79 per cent), but no other abnormalities. The blood uric acid was 1.9 mg. per cent, the blood non-protein nitrogen 30 mg. per cent, and the A/G ratio 3.5/3.0. The Mazzini test was negative. The trichinosis precipitin test was positive in dilutions of 1:1280 (7/15/47) and 1:640 (7/23/47), but the complement fixation test was negative. The electrocardiogram was normal. X-ray examination of the involved joints showed changes essentially indistinguishable from those occurring in advanced rheumatoid arthritis. A chest film showed only old fibrocalcific nodules in the left upper lobe.

The initial diagnosis was that of severe, progressive rheumatoid arthritis. However, because of the fulminant nature of the illness, the marked erythema of the involved joints and the impaired renal function, muscle biopsy was performed. The pathologic report was "acute arteritis."

The patient ran a remittent but low-grade fever ranging between 100° and 101.5° F. until shortly before discharge from the hospital, when the temperature returned to normal. Her joint manifestations were unchanged. She received routine symptomatic treatment. She was discharged from the hospital on October 19, 1947. No follow-up studies are available.

Comment: The diagnosis of one of the "pararheumatic" arthropathies instead of rheumatoid arthritis was suggested clinically by the fulminating course, by the erythema of the involved joints (unusual in rheumatoid arthritis), and by laboratory evidence of disturbed renal function. This suspicion was confirmed by the biopsy findings, although it was not possible specifically to identify the underlying disease.

Case 5. Definite "pararheumatic" arthropathy. Type unknown. Periarthritis and cystic tendonitis. A 38 year old unmarried white female was admitted to the Fourth Medical Division of Bellevue Hospital on April 15, 1947, with the chief complaints of muscle and joint pains.

In December, 1946, the patient had developed an upper respiratory infection which lasted several days but eventually subsided without residual symptoms. In January, 1947, a painful lump appeared on the dorsum of the right wrist. This was diagnosed as a ganglion and was treated with diathermy. Following this she developed myalgias, arthralgias and intermittent swelling of the wrists, elbows, knees and ankles. She also noted increasing stiffness of her fingers and recurrent, tiny, rubbery nodules on the forearms and hands. These musculoarticular symptoms were associated with increasing fatigability and weakness. In March, 1947, she had infrared treatments to her peripheral joints. These increased her pain.

Examination on admission revealed a pale, well nourished woman in no acute distress. The heart and lungs were normal. Both ankles were slightly puffy and tender but showed no redness or increased warmth. There was limited flexion but no swelling of the fingers. Tiny, cystic nodules, 1 to 2 mm. in diameter, were present along the course of many of the tendon sheaths of the hands, wrists and forearms. Some were slightly tender. An erythematous, scaly eruption was present on the dorsum and lateral aspects of the feet and ankles. This was diagnosed by the dermatologic consultant as epidermophytosis.

The red cell count was 4,600,000, the hemoglobin 11.4 gm. and the white cell count 7,200, with 61 per cent neutrophils, 27 per cent lymphocytes, 10 per cent monocytes and 2 per cent eosinophils. Repeated urinalyses were normal except for an occasional 1 plus sugar reaction. The specific gravity was as high as 1.033. The non-protein nitrogen was 28 mg. per cent. The Mazzini test was negative. The A/G ratio was 4.1/2.1. The sedimentation rate was 32 mm./hr. (Westergren). The glucose tolerance test was as follows: fasting, 77 mg. per cent; 30 minutes, 260 mg.

per cent; one hour, 200 mg. per cent; two hours, 143 mg. per cent. X-ray examination of the chest, hands, wrists, knees and ankles was negative.

While in the hospital the patient's complaints continued unabated. For the first four weeks she ran a low-grade fever of about 100° F., with an occasional rise to 101°. The fever then subsided.

Because of the bizarre nature of her musculoarticular complaints and the persistent fever, a muscle biopsy was performed on May 2, 1947. The pathologic diagnosis was "acute interstitial vasculitis of undetermined etiology."

The patient was treated symptomatically with salicylates which relieved her pain. She was discharged from the hospital on June 19, 1947. Follow-up studies are not available.

Comment: The bizarre joint changes in association with fever were not typical of rheumatoid arthritis or of any of the other common rheumatic disorders. The diagnosis of one of the "pararheumatic" arthropathies was established by muscle biopsy. It is interesting to note that this patient's complaints were invariably aggravated by the local application of heat.

Case 6. Diffuse scleroderma. Subacute migratory polyarthritis. A 37 year old woman was admitted to the Fourth Medical Division of Bellevue Hospital on October 3, 1944, complaining of joint pain.

Twenty months prior to admission, in the second month of pregnancy, the patient developed severe pain and swelling of both knees and ankles. There was no antecedent trauma or infection. These symptoms subsided in a few days. During the remainder of her pregnancy she developed intermittent painful swelling of the knees, ankles, wrists and fingers. In the seventh month of pregnancy, labor was induced because of severe toxemia and the child was delivered by forceps extraction. Toward the end of her pregnancy the joint symptoms subsided.

Shortly after delivery, blindness developed rather acutely in the right eye. A retinal detachment was noted. Subsequently the eye was enucleated. Not long thereafter she noted increasing tightness of the skin over the upper sternal region, the face and extremities. Attacks of pain, pallor and numbness of her fingers, precipitated by exposure to cold, occurred in the six month period before admission.

Examination on admission revealed the skin over the upper sternal region, face, fingers, hands and forearms to be pigmented, thickened and taut. There was marked limitation of motion of the fingers, with spindling (figure 3). The blood pressure was 165/70 mm. of Hg. The heart presented no abnormalities. The laboratory data were essentially negative.

The diagnosis was diffuse scleroderma with Raynaud's phenomenon. She was treated symptomatically and was discharged from the hospital on November 4, 1944. She died one year later from an intercurrent infection. No autopsy was performed.

Comment: In this patient, definite evidence of arthropathy preceded the appearance of the cutaneous lesions. No diagnostic problem was encountered at the time she was first seen because the skin lesions were typical of diffuse scleroderma. Had she been seen at the time of her initial joint complaints, when there were no skin lesions, it is doubtful whether the diagnosis could have been made correctly.

Case 7. Lupus erythematosus disseminatus. Rheumatoid-like arthropathy. A 39 year old white female was first admitted to the Fourth Medical Division of Bellevue Hospital on January 4, 1945, complaining of pain and stiffness of the fingers and pain in the chest of three years' duration.

The patient had been well until 1941, when she began to have multiple joint pains. She was seen by a private physician, who could find nothing on physical examination but recorded a white cell count of 6,200 and sedimentation rate of 13 mm./hr. (Westergren).

Early in 1942, she developed persistent chest pains bilaterally, especially on deep breathing. There was no cough, hemoptysis or night sweats. A chest film taken at that time was reported to the patient as showing "arthritis of the spine." At this time also she noticed painful swelling of her finger joints. In June, 1942, she de-

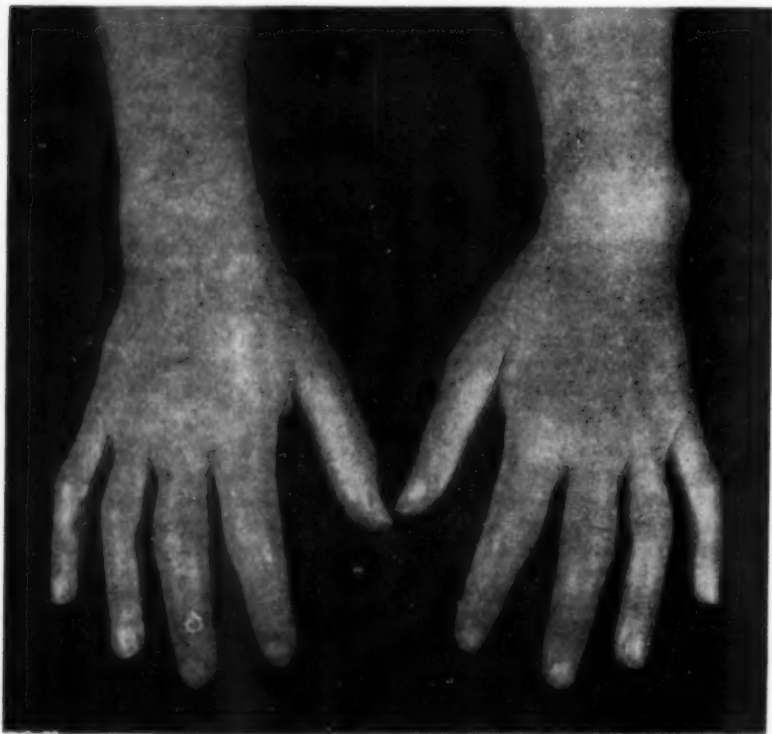


FIG. 3. (Case 6) Diffuse scleroderma. Enlargement of the proximal interphalangeal joints. Smooth, taut, shiny skin, typical of the sclerodermatous process. The joint changes preceded the cutaneous manifestations.

veloped severe chest pains, fever and exertional dyspnea. She was admitted to another hospital, where a diagnosis of acute pericarditis was made. The pericarditis eventually subsided but the patient continued to have chest pain intermittently thereafter.

In the fall of 1944, she developed severe arthralgias involving especially the shoulders, wrists and elbows. Nodular swellings developed on both wrists.

The past history was noncontributory except for migratory polyarthritis at the age of 10.

Examination on admission revealed a well developed, well nourished adult white woman in no acute distress. A loud, widely transmitted systolic murmur was heard at the apex. The heart was not enlarged. The blood pressure was 120/90 mm. of Hg. There were fusiform swelling and slight limitation of motion of the proximal interphalangeal joints of the fingers (figure 4). Soft cystic swellings, 3 cm. in diameter, were present on the dorsum of each hand (figure 4). Smaller but firmer cystic nodules were felt over each of the metacarpophalangeal joints. A right olecranon bursitis was noted (figure 5). There were no subcutaneous nodules. The remainder of the examination was essentially negative except for generalized lymphadenopathy.

The laboratory data were essentially normal except for a persistent leukopenia of from 3,200 to 5,800 white cells. The differential counts were normal. The red



FIG. 4. (Case 7) Lupus erythematosus disseminatus. Rheumatoid-like, spindle-shaped enlargement of proximal interphalangeal joints. Swellings on dorsum of both hands (tenovaginitis).

cell count was 4,090,000 and the hemoglobin, 11.5 gm. X-ray examination of the hands showed "atrophic arthritic changes of the interphalangeal joints." A chest film showed thickened pleura but no cardiac enlargement. Muscle biopsy performed on January 23, 1945, showed nonspecific changes of atrophy and degeneration.

While in the hospital the patient ran a low grade fever ranging between 100° and 102.5° F. She suffered from increasing weakness. The clinical impression was atypical rheumatoid arthritis or "lupus sine lupo." On March 12 a papuloerythematous eruption appeared on the face. The dermatologic consultant considered the lesion suggestive of acute lupus erythematosus disseminatus. The patient was discharged from the hospital on April 7, 1945.

Following her discharge from the hospital the patient continued to run a downward course at home, with high fever, polyarthralgias, and precordial and pleuritic



FIG. 5. (Case 7) Lupus erythematosus disseminatus. Olecranon bursitis, right elbow.

pain. The rash on her face assumed a typical "butterfly" appearance (figure 6). The cutaneous lesions seemed to spread following a course of x-ray therapy.

She was re-admitted to the hospital on November 11, 1945. Physical findings were as noted on the first admission. The only exception was the widespread dissemination of the cutaneous lesions over the face and chest. She was given symptomatic therapy and repeated transfusions. She seemed to improve and was discharged from the hospital on January 14, 1946.



FIG. 6. (Case 7) Lupus erythematosus disseminatus. Typical "butterfly" cutaneous eruption.

Following her second admission to the hospital her condition remained more or less stationary. However, she continued to have severe polyarthralgias, necessitating the frequent use of Demerol, to which she became addicted.

She was admitted again on January 20, 1947, because of an abscess of the right leg that had developed following a self-administered injection of Demerol. Physical findings were as on the previous admissions. The abscess was incised and drained. She continued to run a low grade fever. An anemia with red cell count of 2,850,000 and hemoglobin of 8.4 gm. developed. The white cell count was 6,450. Urinalysis showed a specific gravity of 1.018, with 2 plus albuminuria and a moderate number of red and white blood cells in the sediment. The non-protein nitrogen was 28 mg. per cent. Following the successful drainage of her abscess, she was discharged from the hospital on February 3, 1947. Her course was progressively downward thereafter and she died at home. Autopsy permission was not granted.

Comment: This patient developed polyarthralgias and a chronic polyarthritis resembling rheumatoid arthritis prior to the appearance of the typical "butterfly" eruption of lupus erythematosus disseminatus.

Case 8. Polyarteritis nodosa. Fibrositic symptoms. Rheumatoid-like arthropathy. A 57 year old white male was admitted to the Fourth Medical Division of Bellevue Hospital on July 7, 1944, complaining of pain and stiffness in his arms and legs and profuse sweating of two weeks' duration.

Eight weeks before admission the patient had noted a sudden onset of severe pain and stiffness in the muscles of his upper and lower extremities. The small joints of his hands became swollen. These symptoms persisted until the time of admission.

Past history revealed bronchial asthma of 12 years' duration. System review disclosed a chronic, nonproductive cough of seven months' duration that had recently become more severe. Blood-streaked sputum was noted on two occasions shortly before entry. There had been marked weight loss of unstated amount during the previous several months. For two weeks there had been dyspnea on exertion and swelling of the ankles.

Examination on admission revealed an emaciated middle aged white man in no acute distress. Positive findings were as follows: moist râles and slight dullness at both lung bases posteriorly; a soft systolic murmur at the cardiac apex; slight swelling of the proximal interphalangeal joints of the hands, with poor flexion of the fingers; a weak grip and slight ulnar deviation of the hands; slight limitation of motion of the wrists; 1 plus edema of the ankles, and marked wasting of the muscles of the limbs. The blood pressure was 108/65 mm. of Hg.

The white cell count varied between 10,800 and 22,700, with normal differentials. The red cell count was between 3,500,000 and 4,200,000, with 9 to 10 gm. of hemoglobin. Urinalyses showed 1 plus albumin, with good concentrating power. The Wassermann was negative. The A/G ratio was 2.1/2.7. The non-protein nitrogen was 26 mg. per cent. In a 24 hour urine specimen 465 mg. of creatinine and 155 mg. of creatine were excreted. A precipitin test for trichinosis was positive in 1:1,280 dilution but the complement fixation test was negative. Other laboratory data were essentially within normal limits. A chest film showed slight widening of the supracardiac shadow and diffuse engorgement of both lung fields. X-ray examination of the long bones and skull was negative except for the presence of several punched-out areas in the distal phalanges.

The patient complained of increasing pain and tenderness in his muscles. He ran a low grade, irregular fever with occasional rises to 101° F. A muscle biopsy was reported as showing changes diagnostic of polyarteritis nodosa. The patient

was given supportive therapy, but he lost weight visibly, went progressively downward and died on the eighty-fifth hospital day.

Autopsy was performed and confirmed the diagnosis of polyarteritis nodosa.

Comment: This patient had a sudden onset of myositic symptoms followed by joint swelling. The hands showed changes typical of rheumatoid arthritis. However, the presence of peripheral neuromuscular changes, cachexia, anemia and asthma suggested a different etiologic diagnosis. Muscle biopsy and later the autopsy findings confirmed the diagnosis of polyarteritis nodosa.

DISCUSSION

The preceding review of the literature, our own statistical data and the individual case reports have served to emphasize the high incidence of muscular and articular symptoms in the "pararheumatic" diseases and to stress their frequency as presenting complaints.

It is helpful, as has already been indicated, to classify these symptoms into three major categories: first, myalgias and arthralgias, simulating fibrositis; second, acute and subacute polyarthritis, simulating rheumatic fever; and third, chronic, progressive, deforming polyarthritis, simulating rheumatoid arthritis.

In the first group, the complaints are usually of recurrent pain, tenderness and stiffness affecting various muscles and joints. These symptoms may be present constantly or intermittently throughout the illness. They are not infrequently of long duration. As in true fibrositis, the stiffness and aching can be relieved somewhat by heat, exercise and salicylates. When such complaints are the presenting symptoms, their differentiation from fibrositis is necessary. As a rule this is not a difficult matter. True fibrositis, whether primary or secondary, is usually a self-limited disease, in contrast to the progressive character of the "pararheumatic" diseases. Fever, cutaneous lesions and evidence of visceral involvement do not occur in fibrositis. Their presence in any patient with fibrositic symptoms should at once suggest the possibility of one of the "pararheumatic" diseases as the underlying cause.

In the second group, the characteristic features are the occurrence of attacks of acute and subacute migratory polyarthritis involving both the large and small joints of the extremities. The joints affected are painful, tender, swollen and stiff. Sometimes there is slight local elevation of the cutaneous temperature and redness. Such attacks are of variable duration. They usually last only a few days and disappear without residual changes except for stiffness and aching. On occasions, however, a migratory arthritis may last for months. Salicylates may partially or completely relieve the symptoms but the fever usually is unaffected. It is readily apparent that the course of rheumatic fever may be closely simulated and this diagnosis incorrectly made. This is most likely to occur when a patient with a migratory polyarthritis develops a heart murmur, tachycardia and,

perhaps, pleuritis or pericarditis. The presence of cutaneous eruptions, widespread visceral lesions, and the clinical course of the disease will aid in the differential diagnosis. Sometimes only prolonged observation or pathologic studies will make possible a definite diagnosis.

The third group is the one which we wish to emphasize especially. In this group, a chronic deforming polyarthritis, progressive in nature and resembling rheumatoid arthritis in almost every way (figures 7, 8), is the presenting arthritic complaint. The notion is prevalent that lupus erythematosus disseminatus and polyarteritis nodosa invariably run a fulminating course. While this is often true, it must be remembered that these dis-

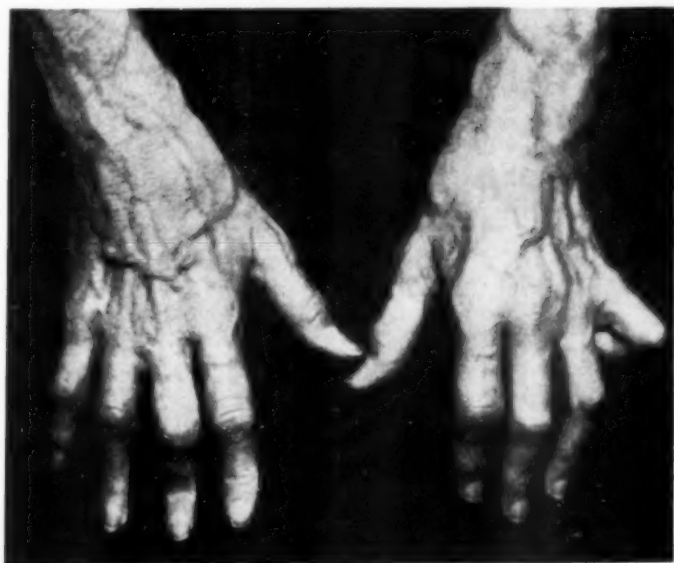


FIG. 7. "Pararheumatic" arthropathy, type unknown. Typical rheumatoid-like arthropathy of three years' duration in a 60 year old woman, whose downward clinical course suggested the diagnosis of one of the "pararheumatic" diseases. Muscle biopsy showed "diffuse arteritis."

eases are not infrequently of long duration. Under such circumstances, symptoms common to other chronic ailments may be found. Failure to recognize that the rheumatoid-like arthropathy present in such cases is really of a different nature may result in serious diagnostic, prognostic and therapeutic errors. Such patients are likely to be subjected to forms of therapy customarily employed in rheumatoid arthritis which are hazardous to patients with one of the "pararheumatic" diseases. Under certain conditions, this may be true of even cortisone and adrenocorticotrophic hormone. The administration of gold salts and other metals, exposure to ultraviolet light

TABLE I
Differential Diagnosis of the Collagen Diseases

Disease	Disseminated L.E.	Periarthritis Nodosa	Diffuse Scleroderma	Dermatomyositis	Rheumatic Fever	Rheumatoid Arthritis
Age	2nd-3rd decades	Any age; 3rd-4th decades chiefly	3rd-5th decades	Any age; chiefly 10-50 years	In 90% onset before 15 yrs. of age	Any age; 3rd-4th decades chiefly
Sex incidence	Females 80%	Males 65%	Chiefly females	Equal	Equal	Slight preponderance of females
Onset	Acute or insidious	Acute or insidious	Insidious	Insidious	Acute, sometimes insidious	Insidious; acute in 10%
Fever	Afebrile to irregular or septic	Afebrile to irregular or septic	Absent until late	Low grade	Low grade to high	Low grade or afebrile
Skin manifestations	Typical erythematous "butterfly" eruption on face; photosensitivity	Erythematous, purpuric or maculopapular eruption in small number of cases	Edema, induration, pigmentation and atrophy of the skin	Noncircumscribed, erythema; occasional hypopigmentation; photosensitivity	In over 10% of cases, erythema nodosum, erythema multiforme, marginatum	Poecilia in 2-3% of cases
Cardiac manifestations	Atypical verrucous endocarditis in 30-50% of cases (clinically silent); pericarditis; other myocardial abnormalities	Involvement of coronary arteries may lead to angina, infarction, congestive failure; pericarditis; electrocardiographic abnormalities	Electrocardiographic abnormalities, arrhythmias, conduction disturbances	Tachycardia, electrocardiographic abnormalities, circulatory failure	Typical valvular involvement; pancarditis frequent	Clinical evidence of rheumatic heart disease in a small number of cases; pathologically as high as 50%
Gastrointestinal manifestations	Uncommon; sometimes pain, vomiting, ascites	Abdominal pain, vomiting, bleeding	Dysphagia; esophagus and small intestine involved	Uncommon	Abdominal pain common	Anorexia, constipation
Renal manifestations	Hypertension; nephritis or nephrosis simulated; uremia	Hypertension; nephritis simulated; uremia	None	Uncommon; sometimes albuminuria and hematuria	None (glomerulonephritis in 5% of cases)	None

TABLE I—Continued

Disease	Disseminated L.E.	Periarteritis Nodosa	Diffuse Scleroderma	Dermatomyositis	Rheumatic Fever	Rheumatoid Arthritis
Splenomegaly	Occurs	Occurs	None	Unusual	None	Sometimes present
Lymphadenopathy	Common	Occasionally	None	None	None	Common
Involvement of serous membranes	Common	Uncommon	None	Rare	Not common	None
Fundoscopic findings	Hemorrhages, fluffy exudates, peripapillary edema	Hemorrhages	Normal	Normal	Normal	Normal
Arthropathy	In almost all cases	In 35% of cases	In over 50% of cases	Common	Acute migratory polyarthritis; no permanent joint changes	Chronic, progressive, symmetrical polyarthritis with deformity
Subcutaneous nodules	None	In about 20% of cases	None	None	In about 20% of cases	In about 20% of cases
Laboratory findings	Leukopenia, anemia, elevated acid rate, sometimes thrombocytopenia, L.E. cell	Leukocytosis with eosinophilia (30%); anemia, elevated ESR; thrombocytopenia sometimes	Anemia, normal acid rate	Eosinophilia in 25%; elevated acid rate	Leukocytosis; elevated acid rate	Leukocytosis; elevated acid rate when disease is active; anemia common
Miscellaneous features	Convulsions	Polyneuritis	Calcinosis	Creatinuria, calcinosis	Chorea	Paroschesias
Prognosis	Almost always fatal; death from toxemia, intercurrent infection, cardiac failure, or uremia	Recovery unusual; death from renal insufficiency, cardiac failure, intercurrent infection	Long duration; death from malnutrition, intercurrent infection, cardiopulmonary failure	Mortality 50-60% in 1-2 yrs.; death from paralysis of respiratory muscles, cardiac involvement, intercurrent infection	Mortality less than 5% in acute phase; ultimately death from the sequelae of valvular disease	Mortality almost nil; morbidity high

and sunlight, fever therapy, x-ray therapy and removal of foci of infection in patients with the "pararheumatic" diseases are known sometimes to cause a grave exacerbation of symptoms with a rapidly fatal termination. We are indeed very cautious in making a diagnosis of atypical rheumatoid arthritis or of fulminating rheumatoid arthritis. We feel that many of these cases are, in reality, "pararheumatic" arthropathies.

It has not been possible, in our experience, clinically to differentiate the muscular and articular manifestations of the various "pararheumatic" dis-



FIG. 8. Lupus erythematosus disseminatus. X-ray of hands, showing osteoporosis, periarticular soft tissue swelling, narrowing of the proximal interphalangeal joints, and narrowing or obliteration of the carpal joints. Findings indistinguishable from those occurring in rheumatoid arthritis. Patient had typical cutaneous lesions. Autopsy not obtained.

eases. There are no identifying characteristics that can serve to distinguish the arthropathy alone as it occurs in lupus erythematosus disseminatus, polyarteritis nodosa or the other diseases in the group. For these reasons, unless it is possible to establish the correct diagnosis on clinical or pathologic evidence, we employ the tentative, noncommittal term of "pararheumatic" arthropathy until more precise identification is made. The differential diagnostic features of the various diffuse collagen diseases are listed in table 1.

In general, the diagnosis of "pararheumatic" arthropathy should be suspected: (1) in a patient with fibrositic complaints who develops constitu-

tional symptoms and signs, especially unexplained fever; (2) in a patient with recurrent, acute or subacute polyarthritis, rheumatic-like or rheumatoid-like, which is of unusual duration, the course of which is progressively downward or fulminating, or in whom signs of visceral lesions and/or involvement of the serous membranes develop; (3) in patients with chronic, progressive, deforming polyarthritis with a fulminating course; (4) in patients with so-called "atypical" rheumatoid arthritis who do not, in a reasonable period of time, develop features distinctive of typical rheumatoid arthritis; and (5) in patients with muscle and joint pains or arthritis occurring in association with bizarre cutaneous lesions.

In all such instances, further clinical investigations, laboratory studies and muscle biopsy are warranted to establish a definite diagnosis. Above

TABLE II
Rheumatoid-like Arthritis

Rheumatic Diseases Which May Be Confused with Rheumatoid Arthritis

Arthritis due to infection

Arthritis due to gonococcal infection

Arthritis due to lymphopathia venereum

Arthritis due to tuberculous infection

Arthritis due to rheumatic fever

Arthritis due to direct trauma

Arthritis due to gout

Neurogenic arthropathy

Tabetic arthropathy

Fibrositis

Diseases in which arthritis, arthropathy or arthralgia is frequently associated:

Dermatomyositis

Diffuse scleroderma

Lupus erythematosus disseminatus

Polyarteritis nodosa

Reflex dystrophy (shoulder-hand syndrome)

Reiter's syndrome

all, the prognosis should be guarded and the patient not subjected to hazardous therapy.

The difference between "atypical" rheumatoid arthritis and "rheumatoid-like" arthropathy must be kept in mind. Rheumatoid arthritis sometimes exists as an irregular symptom-complex of variable duration before its characteristic features make their appearance. This is "atypical" rheumatoid arthritis. Cases included in this category are those with mono-articular or asymmetrical joint involvement; those having an onset with fibrositis, bursitis, tendonitis or severe osteoporosis; and those with an acute onset of migratory polyarthritis resembling rheumatic fever. When such cases are followed for a sufficiently long period of time, the typical clinical picture of rheumatoid arthritis will eventually emerge.

"Rheumatoid-like" arthropathy is an arthropathy resembling rheumatoid arthritis but occurring in other diseases. Almost any one of the arthritides

may simulate rheumatoid arthritis. The commonest of these are listed in table 2.

One additional matter is worthy of comment. The observation that rheumatoid arthritis, rheumatic fever, diffuse scleroderma, dermatomyositis, lupus erythematosus disseminatus and polyarteritis nodosa share, in common, primary pathologic involvement of connective tissue has led some observers to infer that these diseases are etiologically related. Unless this can be definitely established in the future, such an inference would appear to be unwarranted by the information now available. It has been demonstrated repeatedly that the capacity of connective tissue to react to injury is limited to but a few basic patterns. It is inevitable, therefore, that the morphologic alterations produced by these diseases should bear some resemblance to each other. To deduce an etiologic relationship from this pathologic similarity seems to be unjustified at this time.³⁴ In his recent excellent review, Ehrlich³⁵ has reemphasized the fact that the collagen diseases are etiologically heterogeneous. He feels that the common denominator of the various collagen diseases "lies in their pathogenesis or, more precisely, in the production by these diseases of abnormal gamma globulins apparently by plasma cells causing injury of the general mesenchyme." The discovery by Hench and his co-workers³⁶ of the effectiveness of cortisone and ACTH in the treatment of the collagen diseases cannot help but lead one to speculate on the rôle of the pituitary-adrenal axis in the etiology and pathogenesis of these diseases.

SUMMARY

Rheumatic fever, rheumatoid arthritis, lupus erythematosus disseminatus, polyarteritis nodosa, diffuse scleroderma and dermatomyositis are currently recognized as systemic alterations of the connective tissue. While the first two of these diseases are usually easily diagnosed, the four latter ones may present protean manifestations, bizarre clinical features, and difficult problems in differential diagnosis.

To emphasize this clinical differentiation, the terms "rheumatic" and "pararheumatic" have been applied to rheumatic fever and rheumatoid arthritis on the one hand, and lupus erythematosus disseminatus, polyarteritis nodosa, diffuse scleroderma and dermatomyositis on the other. As a corollary, the arthropathy noted in these two groups of diseases is designated as "rheumatic" and "pararheumatic," respectively.

The incidence of musculoarticular manifestations in the "pararheumatic" diseases is high and the presenting complaints are often of this nature.

Three types of muscular and articular involvement are seen in the "pararheumatic" diseases: myalgias and arthralgias; acute or subacute migratory polyarthritis; and chronic, progressive, deforming polyarthritis. The first type resembles fibrositis; the second may mimic rheumatic fever, and the third may simulate rheumatoid arthritis. It is important that the true

nature of these symptoms be recognized so that errors in diagnosis, prognosis or treatment will not be made.

During the years 1938 to 1947, 36 cases of "pararheumatic" arthropathy were studied. All 13 cases of lupus erythematosus disseminatus presented musculoarticular symptoms. In five of these cases, articular involvement occurred before the appearance of the cutaneous eruption. Muscular and joint manifestations were noted in seven of eight cases of polyarteritis nodosa. In three of these cases the initial complaint was of this nature. The case of dermatomyositis had fibrositic symptoms. In the patient with diffuse scleroderma, pain and swelling of the joints preceded the dermatologic manifestations.

"Pararheumatic" arthropathy should be suspected in patients exhibiting the following: fibrositis associated with fever; an acute or subacute polyarthritis of long duration with a downward course; in fulminating, deforming polyarthritis; in "atypical" rheumatoid arthritis; and in arthritis with bizarre cutaneous lesions.

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ESSENTIAL HYPERLIPEMIA *

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IN hyperlipemia there exists an increase in the neutral fat fraction of the blood lipids. When this increase is of sufficient degree the serum assumes a grossly chylous or milky appearance, in contrast to the clear serum noted with an increased blood cholesterol or phospholipid content. Following Thannhauser's¹ example, the term "hyperlipemia" is now reserved for this increase in neutral fat, whereas an increase in the two other lipid fractions is designated "hypercholesteremia" or "hyperlecithemia."

Physiologic hyperlipemia is seen after the ingestion of fats, with a peak in the fat tolerance curve occurring about three hours after a standard test meal.² It is therefore essential that chemical determinations and observations of serum lactescence be performed on blood drawn in the fasting state. If this single physiologic situation is excluded, hyperlipemia then signifies a pathologic process.

Among the conditions in which hyperlipemia has been noted are renal vein thrombosis; nephrotic stage of glomerulonephritis; lipoid nephrosis; hepatic disease; poisoning with carbon tetrachloride, chloroform and phosphorus; starvation; hypoproteinemia; anoxia; anemia; blood dyscrasias; diabetes mellitus; von Gierke's disease; Niemann-Pick disease; hypothyroidism, and pancreatic disease.

The processes by which hyperlipemia is produced in these disease states are, in general, poorly understood. The hyperlipemia and hypercholesteremia in the nephrotic conditions are thought by Thannhauser¹ to depend in part upon an increased transportation of fat from the depot areas. The physiology of such a process has not been elucidated; however, it may entail a response to the general tissue need for oxygen and nutrition, as would be the case in the hyperlipemia of anemia, cachexia, the blood dyscrasias, hypoproteinemia and starvation. In the group of situations in which "transportation hyperlipemia" exists, Thannhauser has listed uncontrolled diabetes mellitus and von Gierke's disease as outstanding examples. There is a mobilization of fat in an attempt to supply the energy which would ordinarily be derived from adequate carbohydrate metabolism. Treatment of the diabetes relieves the secondary hyperlipemia in that situation. In von Gierke's disease, on the other hand, the underlying pathologic physiology cannot be corrected and the resulting lipemia persists. In hepatic disease, poisoning with carbon tetrachloride, chloroform, etc., a similar deficit in carbohydrate metabolism may be the underlying process leading to fat mobilization. In

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hypothyroidism the lipid disturbance is reflected mainly in the cholesterol and phospholipid fractions, with the neutral fat increase being less consistent and of a lesser degree.³ Hyperlipemia in pancreatic disease was first described in 1864 by Speck⁴ and has been reported occasionally since then. In a recent case report, Klatskin and Gordon⁵ were able to find 10 cases previously reported in the literature. The pathogenesis of the lipemia in this condition has been attributed to pancreatic insufficiency, with altered hormonal control of fat metabolism. This hypothesis is not proved. Chaikoff and his associates^{6a and b} and, more recently, Haanes and György,³⁰ have shown that the lipotropic activity of different pancreatic substances seems to reside in their proteolytic activity releasing bound methionine and choline in the intestine. It is these latter substances which exert the lipotropic action, and the pancreatic material apparently acts only by making them available to the organism. Confusion is added to this problem by the fact that depancreatized dogs show fatty infiltration of the liver but a fall in the blood lipids.

After a consideration of the disease states in which hyperlipemia is found, there remains a group of cases in which hyperlipemia exists as the primary abnormality and no other disease can be found to be present. These are the cases of "essential" or "idiopathic hyperlipemia," a situation in which there appears to be a persistent exaggeration of the physiologic hyperlipemia of fat ingestion. This apparent exaggeration of a normal process led Thannhauser¹ to refer to the disease process as one of "retention hyperlipemia," in which the fault lies in inadequate removal of neutral fat from the blood into the depot areas and organs of fat metabolism.

Since 1932, when Buerger and Grütz⁸ described the case of an 11 year old boy with the syndrome of hyperlipemia, hepatosplenomegaly and a xanthomatous eruption influenced by dietary fat content, 21 cases have appeared in the literature as representing examples of idiopathic hyperlipemia. A review of these reports quickly discloses that there was some dissimilarity between the condition as reported in children and in adults. Eight cases have been described in children 16 years of age or younger,⁸⁻¹⁷ and 13 cases in patients above the age of 20.^{7, 18-24} One of the adult cases will not be included in this discussion, as the available information makes it appear that it actually represented a cast of diabetes mellitus with secondary hyperlipemia.*

* One of the four adult patients described by Thannhauser⁷ was a 34 year old male with weakness, xanthomatous skin lesions, glycosuria, acetonuria, hyperlipemia and a high fasting sugar. The history in this case would indicate that the signs and symptoms of diabetes had been present for at least six months prior to the appearance of the xanthomata. The skin lesions cleared with a low calorie, low carbohydrate diet. No mention was made of the fat content of the diet and no values were given for the blood lipids after dietary therapy. As will be noted later, glycosuria is occasionally present in adults with essential hyperlipemia. In these patients a low fat, low calorie diet with moderate carbohydrate restriction reduced the blood neutral fat to near normal values and prevented glycosuria. The diabetic picture in this case was, however, too strong to be ignored, and the case will be considered as belonging to the group with hyperlipemia secondary to uncontrolled diabetes.

Recently we have had an unusual opportunity to study a case of idiopathic hyperlipemia in a 32 year old physician. The findings in this case will be presented after a résumé of the clinical and laboratory features in idiopathic hyperlipemia in children and in adults.

CLINICAL FEATURES

Idiopathic hyperlipemia has been reported only in Caucasians, and all of the 12 adult patients were males. Two of the eight children were females.* ^{10, 11, 12} A feature frequently noted in children has been a failure of normal growth. In five of the eight reported cases ^{11, 12, 13, 14, 17} the patient was referred to as "malnourished," "undersized" or "sickly." Susceptibility to respiratory infections has also been observed frequently. In only one case was there a picture suggestive of an endocrinopathy. Harslöf's ¹⁷ patient presented the appearance of adiposogenital dystrophy, and required treatment with rather large doses of chorionic gonadotrophin. A brother of this patient was described as showing "infantilism." In adult cases there has been nothing characteristic in the habitus or appearance to suggest endocrine or metabolic dysfunction.

In table 1 the symptoms and physical findings in the reported cases are summarized. In every case there has been present one or more features of the triad of abdominal pain, hepatosplenomegaly and xanthomatous skin lesions.

Skin Lesions: Skin lesions have occurred in one-half the cases reported. The eruptive xanthomata have shown a predilection for appearing first on the extensor surfaces, and were grossly similar to the lesion of xanthoma diabeticorum.⁷ The early lesions were yellowish papules with an inflammatory halo; however, the inflammatory appearance later disappeared, making the gross distinction from the tuberous xanthoma of hypercholesteremia difficult. Histologically, the lesions showed only a few scattered foam cells, and "Touton" cells were absent.^{8, 14, 18, 23} There was a moderate infiltration with polymorphonuclear leukocytes. Hand ²⁴ noted that the secondary xanthomata of diabetes, chronic pancreatitis, lipoid nephrosis, von Gierke's disease, biliary obstruction, myxedema and idiopathic hyperlipemia appear identical. In the cases of Holt et al.^{10, 11} and of Hopgood ²⁰ no actual xanthomata were seen; however, there was a history of vesicular lesions on the extremities, draining cloudy material and subsiding to leave depigmented areas. Holt's case also presented lesions of psoriasis which appeared to be unrelated to the basic disease. The xanthomata drained milky material in the cases of Buerger and Grütz ⁸ and Bernstein.¹³ The draining lesions formerly present in the patients of Holt and Hopgood were probably of this type. The xanthomata of idiopathic hyperlipemia subsided with a low fat diet; the secondary xanthomata of other diseases subsided when the underlying process was corrected.

* References 10 and 11 refer to the same patient as described in a preliminary and final report of the case by Holt, Aylward and Timbres.

TABLE I
Clinical Features in Essential Hyperlipemia

Clinical Features and Effects of Diet	Children Total Cases Reported—8 ^(7,17)		Adults* Total Cases Reported—12 ^(7,18,21)	
	No. of Cases	Comment	No. of Cases	Comment
Xanthomatous skin lesions	4		6	
Subsided with low fat diet	4		3	In 1 case ^(7b) patient did not adhere to diet. In the other 2 cases ^(18,21) no mention was made of diet effect.
Abdominal pain	5		6	
Controlled with low fat diet	5		5	Pain in the other case ^(22b) appeared to be on basis of a duodenal ulcer.
Nausea, vomiting	4		5	Symptoms in one of these cases ^(22a) appeared to be on basis of duodenal ulcer.
Pain suggesting a "surgical" abdomen	1		1	
Hepatomegaly	7		7	
Decreased size with low fat diet	6	In one report ⁽⁹⁾ no mention was made of diet effect	5	One of the Thannhauser patients ^(7a) had enlargement only by x-ray; in one case ⁽²²⁾ no report of diet effect was noted.
Splenomegaly	8		5	
Decreased size with low fat diet	7	No mention of diet effect in 1 case ⁽¹²⁾	2	In 1 case enlargement was only by x-ray ^(7a) ; in the other 2 cases ^(30,22b) no mention of diet effect was made.
Lipemia retinalis	5		4	In 4 cases ^(10,20,22a,22) none was detected. In 4 cases ^(7a,22,22b,22c) no mention was made of looking for the condition.

* 7a, b, c designate the 3 cases by Thannhauser. 22a, b, c refer to the 3 cases reported by Movitt et al.

Abdominal Pain: Abdominal pain has also occurred in 50 per cent of the cases, but has not been of a characteristic type. In some cases it was colicky and related to meals,^{9,16} in some it was an aching discomfort,^{18, 21, 22} and in others there were recurrent episodes of severe abdominal distress unrelated to food and occurring at intervals of days or weeks.^{20, 22} The pain was usually upper abdominal. One child and one adult¹⁹ presented the picture of an acute abdominal emergency, and both were subjected to surgery. In Holt's case¹¹ the child was operated upon at the age of five after she had developed severe abdominal pain, projectile vomiting and a

rigid abdomen. At laparotomy, free yellowish fluid was found in the abdomen, and the duodenum was noted to be grayish. The pancreas was not inspected. At the age of 11 she came under Holt's observation and was seen in several similar attacks. He found that the episodes could be predicted by the blood lipid level. The critical blood fat level was 8 per cent. A few hours after this level was reached she would develop colicky epigastric pain, leukocytosis, vomiting, cyanosis and general collapse. The abdomen would become rigid with distention of the superficial abdominal and thoracic veins. On conservative management, the attack would begin to subside in a few hours coincidentally with rapid enlargement of the liver and spleen. There was also rapid fall in the blood lipid level (1 per cent/hr.) as the hepatosplenomegaly increased. Recovery from the attacks usually occurred in four days, at which time the blood lipids would begin to rise as the liver and spleen regressed in size. Holt and his co-workers found no increase in urinary or fecal fat excretion during the attacks. They were of the opinion that there was a deficit in the mechanism of fat removal from the blood. When the fat reached a certain level (8 per cent in this case), the process was precipitated into action, with rapid deposition of lipid in the spleen and liver causing capsule distention and pain.

In the case of Bloomfield and Shenson,¹⁹ a 28 year old white male had a sudden attack of severe right upper abdominal pain, vomiting and leukocytosis. There was guarding over the upper abdomen but no rigidity, and the liver and spleen could not be palpated. At operation no abnormality was found, and a normal appendix was removed after inspection of the liver, kidney and biliary system. Nine months later the patient was hospitalized with a similar episode of acute abdominal pain. At that time xanthomata were noted, and there was an elevated cholesterol with milky serum; however, the liver and spleen were still not palpable. The patient remained asymptomatic on a low fat diet. These authors stated: "When confronted with obscure, severe abdominal pain, it is worth while keeping the possibility of lipemia in mind, and a glance at the eyegrounds or an inspection of the hematocrit tube may reveal the excess of fat in the blood, and make the diagnosis evident."

Lipemia Retinalis: In lipemia retinalis, the high blood lipid level caused the retinal vessels to present a salmon pink appearance, and it was difficult to differentiate between the arteries and veins. In nine of the cases of idiopathic hyperlipemia, lipemia retinalis was noted. Lepard²⁵ stated that it appeared when the blood fat level reached 3.5 per cent and disappeared when the level fell below 2.5 per cent. However, it has been reported in a diabetic with a blood lipid level of only 1.42 per cent.²⁶ In a recent review, Carfagno and Steiger²⁷ were able to find reports of 63 cases of lipemia retinalis in various conditions, the majority in patients with uncontrolled diabetes. They emphasized the fact that a disproportionate increase of neutral fat, as compared with phospholipid increase, was the important factor leading to

lipemia retinalis. It appeared when the phospholipid to neutral fat ratio was decreased, and disappeared when the ratio returned to normal.

Hepatomegaly and Splenomegaly: Splenomegaly has been present in every case reported in children, and hepatomegaly has been absent in only one patient. In adults, about one-half of the patients showed enlargement of the spleen or liver. In every case in which the patient was followed the

TABLE II
Blood Lipid Values and the Effect of Fat Restriction
(mg. %)

Laboratory Tests	Bernstein et al. ⁽¹²⁾ 6 year old male		Goodman et al. ⁽¹¹⁾ 1 year old male		Harsid ⁽¹⁷⁾ 16 year old male		Hopgood ⁽¹⁸⁾ 26 year old male	
	Regular Diet	1 Month Low Fat	Regular Diet	1 Month Low Fat	Regular Diet	1 Month Low Fat	Regular Diet	1 Month Low Fat
Total blood lipid	4,253	3,159	3,954.0	2,598.0	3,840	3,080		
Total fatty acids			3,115.0	1,900.0			3,370	1,840
Total neutral fat	3,196	2,166			2,671	2,077	3,202	1,612
Total cholesterol			379.0	330.0	596	483	250	204
Free cholesterol	175	129	158.0	114.7	204	229		
Cholesterol esterified	366	428	220.0	215.0			100	118
Total phospholipid	516	436	465.0	368.0	573	520	328	207
Cephalin			0.0	60.0				
Lecithin			452.4	295.9	The low fat diet in this case appeared actually to contain considerable fat.			

Laboratory Tests	(7a) Thannhauser (7b)				Movitt ⁽¹⁹⁾ 48 year old male		Frank and Levitt ⁽²¹⁾ 36 year old male	
	47 year old male		22 year old male					
	Regular Diet	1 Month Low Fat	Regular Diet	1 Month Low Fat	Regular Diet	1 Month Low Fat	Regular Diet	1 Month Low Fat
Total blood lipid					1,060	760	2,164	
Total fatty acids	5,196	480	3,370	1,840				530
Total neutral fat	4,477	275	3,202	1,612				240
Total cholesterol	693	175	250	204	302	230	974	232
Free cholesterol	323	58	150	86	165	138		56
Cholesterol esterified	396	117	100	118	137	92		176
Total phospholipid	810	195	328	207	* 365	300		239
Cephalin } Lecithin }	685	175	290		During the low fat diet, the patient was on inositol for 1 week.			

size of these organs diminished on a low fat diet. Every adult who did not have enlargement of these organs showed xanthomata. One patient with xanthomata had hepatosplenomegaly detectable only by x-ray.^{7a} Another patient had an enlarged liver and spleen with a history suggestive of xanthomata in childhood.²⁰

Family History: Although the investigations have not been thorough, there has been nothing to suggest a familial tendency in any of the adult

cases. A family history suggesting xanthomata or metabolic disease was present in only one case,²³ in which the patient's mother had been diabetic. In three cases the blood of siblings or parents was found to be grossly normal.^{18, 20, 21} Blood lipid determinations on the mother of one patient and the brother of another were within normal limits.²² In children, on the contrary, there has been evidence of a familial lipid disturbance in three of the eight cases. In the case reported by Levy¹⁶ the serum of both parents and a half-brother appeared grossly normal, whereas the serum of a sister was estimated to be "one-fourth fat." This child was asymptomatic and no further studies were done. An eight year old brother of the patient presented by Holt, Aylward and Timbres^{10, 11} was found to have elevated blood lipids, hepatosplenomegaly and lipemia retinalis. The child was asymptomatic. The blood lipids of the mother and a sister were moderately elevated. The strongest evidence of a familial disease was presented in Harslöf's report.¹⁷ Both parents and the two living siblings of the patient showed an elevation in blood lipids. Another brother had died after showing hepatomegaly, lipemia, xanthomata and evidence of an endocrinopathy. A second brother had died after being hospitalized with hepatomegaly and evidence of a blood dyscrasia.

LABORATORY FEATURES

The prominent laboratory abnormality in idiopathic hyperlipemia is an increase in neutral fat, the level varying with the dietary fat. In table 2, cases are presented in which adequate laboratory data are available to permit an interpretation of the effect of diet. Harslöf stated: "Still, the hyperlipemia cannot be completely overcome, neither by dietetic measures nor any other means, and the serum retains its milky appearance." It can be seen, however, that the lipids have returned to normal levels in some of the cases. It would appear that the response of adults may be more complete than that of children. It is noted that there was usually some increase in the cholesterol and phospholipid levels; however, this elevation was of a minor degree when contrasted with the marked elevation of neutral fat. It can also be seen that the cholesterol increase was predominantly in the free fraction, with a resulting decrease in the per cent of cholesterol present as esters.

The grossly milky appearance of such serum is apparently due to a relative insufficiency of phospholipid. Ahrens and Kunkel²⁴ studied the clear high lipid sera of patients with primary biliary cirrhosis. In this condition there was a marked phospholipid increase, with a lesser increase in cholesterol and a minor increase in neutral fat. Enzymatic destruction of serum lecithin by the action of *Clostridium welchii* lecithinase in vitro resulted in a lactescence of the serum closely paralleling the total lipid content. Even in grossly chylous serum, enzymatic removal of the stabilizing effect of phospholipids resulted in greater opacity. These workers also found that serum was milky when the phospholipid total lipid ratio (as determined in their laboratory) was below 0.29 (normal 0.31 to 0.40). The colloidal solution

of lipids became cloudy when the particle size exceeded one-fourth the wave length of visible light.

Urinalysis: Analysis of the urine has revealed no abnormality in patients below 16 years of age. Glycosuria was reported in two cases in adults.^{7, 20} Thannhauser⁷ emphasized the importance of differentiating "idiopathic hyperlipemia accompanied by slight diabetes" from the secondary hyperlipemia of uncontrolled diabetes mellitus. In the former condition, the hyperlipemia responded to a low fat diet but was not affected by insulin; in the latter, insulin corrected the hyperlipemia by control of the diabetes. The occasional glycosuria in adults can then be added to the previously noted features of the disease, which are dissimilar in adults and children. These differences led Thannhauser to refer to the disease in children as "idiopathic (familial) hyperlipemia in children with hepatosplenomegaly and secondary xanthoma," and in adults as "idiopathic hyperlipemia in adults with and without secondary eruptive xanthoma, occasionally accompanied by glycosuria and hepatosplenomegaly."

Blood Sugar Levels: Glucose tolerance tests were recorded in seven of the children, with normal results in six cases. In one case¹³ there was a rather high peak in the curve. The results of a glucose tolerance test were recorded for seven adult cases. Two of these cases²² showed a high spike in the curve, but the other tests were within normal limits. In the five other adult cases only a fasting blood sugar was recorded. The recorded values lay between 100 mg. per cent and 115 mg. per cent in each case except one reported by Thannhauser.⁷ This patient had an original fasting blood sugar of 206 mg. per cent. After a period of a low fat diet the value was 124 mg. per cent.

Sternal Marrow Studies: Sternal marrow examination was done in seven living cases and no abnormality was found in three of these.^{16, 22} In one case there were decreased erythropoiesis and eosinophilia but no foam cells.¹⁷ In the three other examinations foamy cells of the fat storage type were seen.^{18, 21, 22} Chapman and Kinney¹⁵ published the postmortem findings on the patient of Goodman, Shuman, and Goodman.¹⁴ This is the only reported autopsy on a patient with idiopathic hyperlipemia. The vertebral marrow of this child showed only a few scattered foam cells.

Liver and Spleen Biopsies: By hepatic needle biopsy, Movitt et al.²² found the liver cells to be nearly filled with fat vacuoles but no excessive pigment or phagocytized fat. Koszalka and Levin²¹ found the liver architecture to be distorted with abundant fat, groups of foam cells, and lack of cellular uniformity. In the Chapman and Kinney autopsy report¹⁸ central congestion and scattered focal necrosis were noted, but no foam cells. The spleen in this case contained scattered foam cells similar to the large "Schultz" cell of hyperlipemia due to diabetes. The other microscopic examination of the spleen was reported by Franklin and Avery,¹² who found no abnormal cells but some minute patches of fat-staining material extracellularly.

Other Laboratory Procedures: Numerous other laboratory procedures have been performed on patients with essential hyperlipemia. They are too numerous to examine in detail, but no significant or consistent abnormality has been noted.

In each case it appeared that sufficient study was performed to rule out the conditions causing secondary hyperlipemia. In table 3 the results of

TABLE III
Laboratory Examinations

Test	No. of Cases	Results	References*
Basal metabolism	14	No significant abnormality	8, 11, 13, 17, 18, 19, 21, 7b, 22, 23, 24
Blood urea nitrogen	5	Normal	12, 17, 18, 22b, 22c
Non-protein nitrogen	2	Normal	11, 14
Intravenous urogram	3	Normal	17, 18, 20
Serum bilirubin	6	Normal	11, 14, 19, 20, 22b, 22c
Thymol turbidity	3	Elevated in 1 case ^(7b)	22, 22b, 22c
Cephalin flocculation	5	Normal	20, 21, 22b, a, c
Bilirubin excretion	1	Normal	11
Hippuric acid synthesis	1	Normal	21
Galactose tolerance	1	Normal	13
Levulose tolerance	1	Normal	11
Bromsulfalein excretion	4	Normal	21, 22
Serum phosphatase	5	Normal	14, 17, 20, 21, 22c
Serum prothrombin	3	Normal	21, 20, 22b
Serum protein and A/G ratio	9	Slightly decreased ratio in 2 cases ^(21, 22b)	11, 14, 17, 19, 21, 22b, a, c
Serum amylase	8	Normal	14, 18, 19, 20, 21, 22a, b, c
Serum lipase	4	"Not decreased" in 1 ⁽⁹⁾ "None" in 1 ⁽¹⁰⁾	9, 14, 18, 20
Urine diastase	3	Negative	11, 17, 18
Stool fat	7	No excess (neutral fat fraction increased in 1 case ⁽¹⁷⁾)	11, 13, 14, 17, 18, 21, 22c
X-ray—bones, skull	9	Negative	11, 12, 14, 16, 17, 19, 20, 21, 23
X-ray—GI tract	7	Duodenal ulcer deformity in 3 cases ^(21, 22a, b)	11, 14, 16, 21, 22a, b, c
X-ray—gall-bladder	3	Negative	18, 20, 22c
Stool for ova and parasites	3	Negative	11, 14, 22c
Gastric analysis	2	Normal	16, 21
Porphyrin excretion	1	Not increased	21
Electrocardiogram	3	Normal	17, 22c, 23
Electrolyte studies (CO ₂ , Na ⁺ , Cl ⁻ , Ca ⁺ , K, P, Mg)	—	Various determinations by different workers—all normal	11, 13, 14, 17

* 7a, b, c designate the 3 cases reported by Thannhauser. 22a, b, c refer to the 3 cases reported by Movitt et al.

various laboratory procedures are summarized. There is a remarkable lack of abnormal findings.

CASE HISTORY

A 32 year old white male physician was admitted to the U. S. Naval Hospital, Oakland, California, on October 13, 1951, with the complaint of intermittent, aching, right upper quadrant abdominal pain. While serving overseas in 1945 he had experienced his first symptom referable to the abdomen or gastrointestinal system when he had a short period of loose foamy stools. He was thoroughly studied for parasitic and bacillary infestation at that time, with negative results. He was then well until 1948, when he experienced watery diarrhea with some blood and mucus in the stools. Amebiasis was established as the diagnosis and he became symptom free in October, 1948, following a course of carbarsone and Diodoquin.

In October, 1949, he first noticed dull, aching right subcostal discomfort exaggerated by fatty foods. There was no associated diarrhea or other change in bowel function. A month after this symptom began he was hospitalized because of an acute upper respiratory infection, and liver function studies were performed when the serum was noted to be grossly milky in appearance. The serum bilirubin, cephalin cholesterol flocculation and bromsulfalein excretions were reported to him as being normal. However, the serum cholesterol was elevated, and the thymol turbidity was 17 units. After a few weeks on a moderately restricted fat intake the symptoms subsided. The gross appearance of the serum remained essentially unchanged. The patient experienced only occasional discomfort from that time until January, 1951, when there was a recurrence of constant, dull, aching right upper abdominal pain. Fatty foods would cause some sharp pain in this area, with some associated nausea. This complaint prompted his admission to a hospital in February, 1951, when the only remarkable finding at physical examination was a tender liver, palpable 2 cm. below the right costal margin. Many laboratory and roentgenographic procedures, including stool examinations for ova and parasites, serum lipase and amylase determinations, gastrointestinal x-rays and blood lipid studies, were performed. The results were within normal limits except for a thymol turbidity of 17 units and an elevation of the serum lipids with opalescence of the blood serum. Because of the previous history of amebiasis he was given a course of emetine, and returned to duty on a low fat diet. He continued to have mild, nagging abdominal discomfort and was hospitalized in April, 1951, with an otitis media and exacerbation of the abdominal pain. After his recovery from the ear infection the abdominal complaint was less marked and he again returned to duty. He had some periods when he was asymptomatic on a fat restricted diet at home; however, a dull discomfort was usually noticeable. In September, 1951, he had an exacerbation of his symptoms coincident with an upper respiratory infection and was again hospitalized. The findings were essentially unchanged from the previous hospitalization; however, there was some inconstant radiation of pain into the anterior chest bilaterally and into the right lower quadrant. He had noted no upset in bowel function. The diagnosis of idiopathic hyperlipemia was entertained, and he was transferred to the U. S. Naval Hospital, Oakland, California.

When admitted to this institution he had been on a strict low fat diet for six weeks and had taken oral methionine, inositol and choline for two months. On physical examination the patient was a well developed, somewhat pallid appearing white male. The height was 76 inches and the weight was 198 pounds. The liver, which was slightly tender, smooth and firm, was palpable 2 cm. below the right costal margin on inspiration. The spleen was felt at the costal margin. The remainder of the examination was not remarkable; there were no lipemia retinalis and no skin lesions suggestive of xanthoma. The patient was placed on a low fat diet containing 428 gm. of carbohydrate, 80 gm. of protein, and 25 to 40 gm. of fat, with approximately 100

mg. as cholesterol. He had only occasional vague right upper quadrant discomfort on this regimen and was given no specific medication. The liver could not be palpated after his first week in the hospital.

Laboratory Procedures: Routine laboratory procedures, including complete blood counts, bleeding time, clotting time, platelet counts, a blood Kahn test and a chest x-ray, were within normal limits.

Lipid Studies: The blood lipid values of this patient are summarized in table 4. It can be seen that the greatest lipid increase was in the neutral fat fraction. There

TABLE IV
Lipid Values

Date	Total Lipid* Mg. %	Fatty Acids* Mg. %	Mg. % of P. Phospholipid*	Neutral Fat Mg. %	Cholesterol* Mg. %	Free Cholesterol* Mg. %	Ester Cholesterol* Mg. %	Comment
2-27-51	2,067	1,350			653.6	212.0	441.0	Determinations, courtesy Capt. H. L. Weaver, MC, USN; Navy Med. Unit, Tripler Army Hospital
7-18-51	1,971	1,650			374.0	148.0	226.0	
10-12-51					420.0	278.0	142.0	
10-25-51					328.0	217.0	111.5	
10-30-51	895		11.3		320.0	182.4	137.6	Low fat diet 6 weeks "Methischol" 2 months
11- 6-51					315.0	160.7	154.3	
11-15-51					284.0	133.5	150.5	
11-21-51	760		10.0		314.0	144.8	169.2	
12- 5-51	760	527.7	9.3	254.9	320.0	150.4	169.6	Operation
12-21-51	558		10.5		356.0	165.6	190.4	
1-29-52	1,417	1,053	10.4	745.0	472.0	254.0	218.0	Home low fat diet for 1 month
2- 4-52	1,491							
2-15-52	904		12.0					Hospital diet for 15 days

* Methods: Total Lipid—Kaiser and Kagan modification of Stoddard and Drury method, *Analyt. Chem.* **23**: 1879, 1951.

Fatty Acids—Method of Stoddard and Drury, *J. Biol. Chem.* **84**: 741, 1929.

Phospholipid—Method of King, *Biochem. J.* **26**: 292, 1932.

Neutral Fat—Formula of Thannhauser and Reinstein, *Arch. Path.* **33**: 646, 1942.

Cholesterol—Modification of Bloor method, *J. Biol. Chem.* **52**: 191, 1922.

was some attendant increase in the cholesterol values, with relatively normal phospholipids. In this case, as in others previously mentioned, the cholesterol increase was mainly in the free fraction. The high total lipids in February and July, 1951, were obtained while the patient was on a normal diet. The marked effect of restriction of dietary fat was evident, with an increase in lipid values on a home low fat diet, and a return toward normal on a hospital diet. The opalescence of the serum varied directly with the blood lipid level. When the lipids were low during the hospital diet, the serum was not appreciably opalescent. Figure 1 shows milky appearance after one month on a fat-restricted diet at home.

Renal Studies: Repeated urinalyses were normal; the blood urea nitrogen was 10.2 mg. per cent and 12.8 mg. per cent; the blood creatinine was 1.29 mg. per cent; the Addis count on a 24-hour urine specimen was normal.

Liver and Biliary Function: An oral cholecystogram showed a normally functioning gall-bladder. Serum bilirubin was 0.04 mg. per cent in one minute and 0.3 mg. per cent at 30 minutes. The gamma globulin was 0.9 and 1.2 gm. per cent (normal, 0.7 to 1.25). Total serum protein was 6.7 gm. per cent, with 3.5 gm. per cent albumin, 1.1 gm. per cent alpha globulin, and 0.9 gm. per cent beta globulin. Alkaline phosphatase was 1.18 Bodansky units, and acid phosphatase was 1.4 Gutman units. Hippuric acid excretion after the oral administration of 5.9 gm. of sodium benzoate was

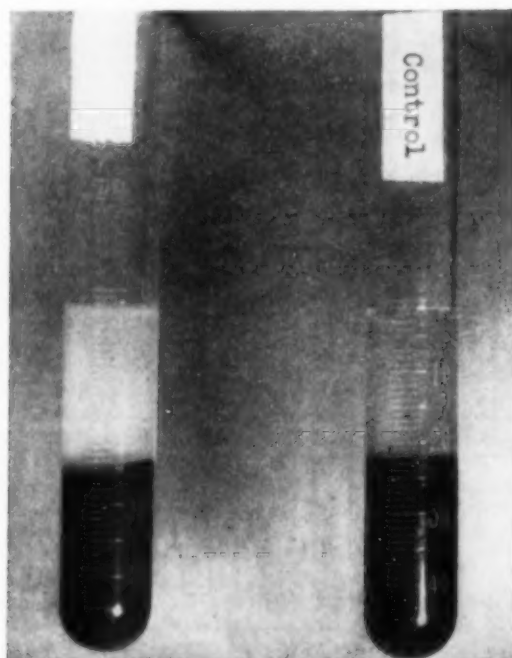


FIG. 1. Lactescence of serum of author's patient as compared with control serum after one month on home "low fat diet." Total lipid = 1,417 mg. %; neutral fat = 745 mg. %.

3.53 gm. as sodium benzoate (normal, 3.54 gm.). The thymol turbidity was persistently elevated to between 13.7 and 19.5 units, the higher values prevailing when serum lipid values were high. The zinc turbidity was determined in an attempt to rule out the effect of high blood lipid. The zinc turbidity was normal (5.3 units). Cephalin cholesterol flocculation was negative at 24 hr. and \pm or 1+ at 48 hours.

Endocrine Metabolic Studies: The basal metabolic rate was minus 11 and minus 14. The protein-bound iodine was 7.0 gamma per cent (normal, 3.5 to 8). The glucose tolerance values were: fasting, 97 mg. per cent; one-half hour, 183 mg. per cent; one hour, 123 mg. per cent; one and one-half hours, 72 mg. per cent; two hours, 86 mg. per cent. Three separate determinations of 17-ketosteroid excretions showed an average of 13.9 mg./day (normal, 8 to 18). The total circulating eosinophil count

was 117; the response to the injection of adrenalin was poor, with a drop to 105 in the count of two hours. The urinary excretion of porphyrins was not increased.

Gastrointestinal and Pancreatic Studies: A gastrointestinal series was normal. On a plane film of the abdomen no intraabdominal calcifications were visible. Repeated stool specimens for ova, parasites and occult blood were negative. The serum lipase determination was 0.04 ml. as .05 sodium hydroxide. Serum amylase was 46 mg. per cent as glucose during a period of most marked abdominal pain. A duodenal drainage showed the presence of lipase, and the aspirated material contained a moderate amount of mucus, no blood and no cholesterol crystals. A gastric sample was normal and titrated to 46 units total acid, with 10 units free hydrochloric acid. The feces contained 2.6 gm. of fat per 100 gm. of wet stool.

Tissue Studies: A needle aspiration of sternal marrow was performed. Microscopic examination disclosed a normal marrow with no lipoid-containing cells.

Although the patient was essentially asymptomatic on a low fat diet, deviations from this routine would produce abdominal discomfort and he desired an exploratory laparotomy. On December 6, 1951, the abdomen was opened via a right rectus incision. The liver, biliary system, spleen, stomach and duodenum were normal upon inspection. On exploration of the small bowel there was a paraduodenal hernia sac on the left side of the abdomen containing the majority of the small bowel. The internal hernia was reduced and the sac obliterated. Exploration of the remaining viscera revealed no abnormality. A 1.5 cm. wedge biopsy of the liver was taken and a long, normal appearing appendix removed.

The hematoxylin and eosin-stained section of the liver showed no abnormality of the parenchymal cells or hepatic architecture, and the section stained for glycogen was normal. Tissue stained for fat with Scarlet R showed no increased fat or evidence of fatty metamorphosis. No "foam cells" were seen. The appendix showed only slight fibrosis and adipose replacement microscopically.

Recovery from the operation was uneventful. It can be seen in table 4 that the lowest total lipid value occurred after the operation, with its attendant intravenous feedings and period of very low dietary fat intake. There was no appreciable change in the patient's symptoms after operation. He remained asymptomatic on a low fat diet, but would notice aching upper abdominal discomfort on any excursions from this. He was granted a 30-day leave from the hospital, and returned having some constant dull pain. His lipid values had increased, and the opacity of the serum at that time can be seen in figure 1. On a hospital diet he again was asymptomatic as his blood fat declined.

We have been unable to establish any relationship between the paraduodenal hernia and the symptomatology. In Iason's text on hernia²¹ there is an excellent discussion of internal hernia of this type. This patient had a classic left paraduodenal hernia with the inferior mesenteric vein in the anterior fold of the sac. The origin of these lesions is apparently a postnatal protrusion into the preformed paraduodenal fossa of Landzert. The symptomatology varies from signs of acute intestinal obstruction to vague abdominal symptoms. Not infrequently the anomaly is first noted at autopsy. There is no mechanism apparent to us by which such a lesion could produce hyperlipemia, and surgical correction had no effect on the blood lipid picture.

In this case there is seen the susceptibility to respiratory infections; the abdominal pain; the normal hepatic, pancreatic, renal and endocrine studies; the slight hepatomegaly, and the beneficial result of dietary fat restriction. Lipemia retinalis and xanthomatous skin lesions were not seen.

No family history could be obtained in this case. He was an only child, and his mother had died at a rather early age. His father had a coronary thrombosis in his fifth decade. The blood of the patient's two children (aged six and eight) was grossly normal, and cholesterol determinations at another hospital were normal.

PATHOGENESIS AND TREATMENT

As was previously mentioned, Thannhauser¹ classified this condition as a retention hyperlipemia. The mechanism of the sluggish removal of fat from the blood was not understood; however, he is of the opinion that an anatomic or functional change in the capillaries is the most acceptable hypothesis. The fat increase appears to be confined to the blood, as the fat content of the liver was not increased in the autopsy report of Chapman and Kinney.¹⁰ Holt, Aylward and Timbres¹¹ noted normal respiratory quotients and ketonuria during fasting as indications of normal fat metabolism in their patient.

Bernstein et al.¹² found nothing remarkable in the specific dynamic response, respiratory quotient, nitrogen excretion and ketone production of their patient. In Goodman's case¹⁴ no lipase was detected in the serum, but no humoral factor has been implicated in the other reports. Holt and his group¹¹ gave their patient blood transfusions in an attempt to supply some unknown substance lacking in the patient's blood. Their results were equivocal. Only Harsl f's patient¹⁷ showed evidence of an endocrinopathy; however, Holt recorded the lowest lipid level in his patient just after her first menstrual period. In this connection Eilert²² studied postmenopausal females and found that estrogen therapy produced an elevation of the serum phospholipids with a decline in cholesterol. During the current "adrenal era," attention has been focused on the effect of cortisone and adrenocorticotrophic hormone in producing an elevation of serum phospholipid and cholesterol.²³ According to Levin and Farber,²⁴ fat mobilization to the liver is effected through circulating cortisone and some trigger hormone from the pituitary. In adrenalectomized animals, adrenocorticotrophic hormone alone is ineffective in this respect.

Being innocent of knowledge as to the etiology of this condition, our treatment is solely dietetic. Holt and his co-workers¹¹ gave lecithin, choline, thyroxin, insulin, liver extract, pancreatic substance and blood transfusions, with no noticeable effect in essential hyperlipemia. If the diagnosis is firmly established, the patient will respond well to a diet low in fat and cholesterol. Insulin is not indicated for the occasional glycosuria.

PROGNOSIS

The only reported autopsy on a patient with idiopathic hyperlipemia was performed on a child who died of an intercurrent illness.¹⁰ The findings in this case have been previously discussed. We are left with the impression

that this condition has a good prognosis, but there is a natural curiosity concerning the likelihood that these people may develop early atherosclerotic lesions. In the autopsied child no lesions were found, and there has been no apparent predisposition for atherosclerosis in the other reported cases. Since long term follow-ups on these patients have not been reported, a better approach might be to examine the current work on the atherosclerotic problem. Gertler, Garn and Lerman³⁵ found that patients with coronary artery disease showed an increase in the cholesterol/phospholipid ratio. There was some increase in the phospholipid values, but the cholesterol, and especially the ester fraction, was disproportionately elevated. In our patient, and in others, the increase in cholesterol has exceeded the phospholipid rise; however, the cholesterol elevation has been mainly in the free fraction. Ahrens and Kunkel studied patients with the clear high lipid sera of primary biliary cirrhosis. In this condition there are marked cholesterol and phospholipid increase, slight neutral fat elevations and frequent xanthomatosis. They found an absence of remarkable atherosclerosis in conjunction with a high blood lipid level, xanthoma and a normal cholesterol/phospholipid ratio. Nephrotic patients, in contrast, were found to have an increased cholesterol/phospholipid ratio with their well known susceptibility to premature atherosclerosis.^{36, 37} It would appear from these reports that relative deficiency of phospholipid is of importance in the genesis of atherosclerosis. The emulsifying effect of phospholipid was previously discussed as being of prime importance in determining if high lipid serum is clear or milky. In essential hyperlipemia the serum is chylous with a low phospholipid/total lipid ratio.

In a further attempt to determine if these patients show an increased tendency to atherosclerosis, the effect of intravenous heparin was observed. Hahn³⁸ first noted that intravenous heparin decreased the serum lactescence in alimentary hyperlipemia. Other anticoagulants did not produce this effect.

This phenomenon has been studied by subsequent workers.³⁹⁻⁴² It begins *in vivo*, but will continue *in vitro*. Apparently the mode of action is by a reduction in surface tension. Heparin caused some increased clumping of the chylomicrons, but a decrease in the chylomicron count. Opacity decreased without a significant change in the quantitative blood lipids.

Heparin Injection: Block, Mann and Barker⁴² studied the effect of intravenous heparin in clearing the alimentary hyperlipemia of normal and atherosclerotic patients. We closely followed their method in the study of our patient and a small group of controls. This consisted of giving the fasting subject a fat meal of milk and cream containing 97.26 gm. of fat; 3 mg. of heparin was given three hours after this meal. Blood samples were drawn in the fasting state, prior to the heparin injection and 15 minutes after the heparin. Translucence of the plasma was measured on a Coleman Junior Spectrophotometer one hour after the last specimen was drawn. Subtract-

ing the optical density of the fasting specimens, the other two values were used to calculate the per cent of clearing produced by the heparin. Our results were similar to those of Block's group. We ran only enough controls to determine if our results were comparable to their findings. Our results are compared with those of the Block group, as follows:

	Cases	Average % Clearing
Block et al.	23 normal males	74.0
Control	3 normal males	72.0
Block et al.	27 males with atherosclerosis	38.0
Control	1 male with atherosclerosis	39.2
Author's patient	Essential hyperlipemia	40.2

The results of this study might be another indication that patients with idiopathic hyperlipemia will show a susceptibility to atherosclerosis. This must be accepted with caution, however, as the Block group found one of their "normal" patients showed only 28 per cent clearing. Two of their atherosclerotic group showed 100 per cent clearing. We consider, however, that the weight of evidence favors the opinion that patients with essential hyperlipemia run an exaggerated risk of premature atheromatous vascular lesion.

Recently, two reports have appeared which would suggest pancreatitis as another complication of essential hyperlipemia. The patient of Klatskin and Gordon⁸ had a history of yellowish papular skin lesions prior to the onset of definitely diagnosed pancreatitis. Xanthomatous lesions had reappeared when he had recurrent pancreatitis and were seen by these observers four years after the original attack. They hypothesized that fat emboli might have caused the pancreatitis. Although there was an exaggeration of hyperlipemia and xanthomatous lesions at the time of attacks of pancreatitis, there were also asymptomatic periods when there was marked lipemia. In general, lipemia subsided after the acute episodes. Hyperlipemia has been thought to be the result of pancreatic damage, and the evidence that it existed prior to pancreatic disease in this case was based solely on the history of skin lesions prior to his first attack.

If pancreatic damage can cause hyperlipemia, it would appear adequate to explain the hyperlipemia when this patient was observed.

Poulsen⁴⁴ presented a case with hyperlipemia, hepatomegaly and definitely diagnosed pancreatitis. In this case, the patient had had symptoms for two years prior to the reported observations. There was an adequate period for hyperlipemia to appear secondary to pancreatic damage. The long-term observation of patients with essential hyperlipemia is essential before it will be known whether hyperlipemia in these cases is the cause or the result of the pancreatitis.

SUMMARY

The clinical and laboratory features of essential or "idiopathic" hyperlipemia have been presented and another case report added to the literature.

One or more features of the triad of hepatosplenomegaly, abdominal pain and xanthomatous skin lesions characterize the disease clinically. Elevated blood neutral fat with a lesser elevation in serum cholesterol and phospholipid is the biochemical abnormality. The elevation of blood lipids produces a lactescence of the serum which aids in the rapid diagnosis of the disease. It is a disease which is diagnosed largely by exclusion, and which responds well to simple dietary fat restriction.

It is seen that varied manifestations of this condition make it an important, although rare disease. The patient who primarily develops the skin manifestation presents himself to the dermatologist. The patient with the severe abdominal pain of essential hyperlipemia may be saved from a needless laparotomy if the surgeon will note the milky hematocrit tube. The patient with obscure hepatosplenomegaly and vague abdominal pain will puzzle the internist and pediatrician until plasma lactescence or lipemia retinalis is observed.

The history and laboratory findings of a case of essential hyperlipemia have been presented. The beneficial effect of dietary fat on the lipid values and symptomatology was prominent. Tests for endocrine, metabolic, renal, hepatic, pancreatic and gastrointestinal abnormalities have been summarized and discussed. Biopsy material from the bone marrow and liver was examined and a laparotomy performed. The incidental operative finding of paraduodenal hernia was discussed. The prognosis in the disease was considered and an attempt was made to determine the likelihood of premature atherosclerosis in these patients. Our studies and present day evidence would indicate that the patient with essential hyperlipemia is more likely to develop atherosclerosis than his counterpart with normal fat absorption, deposition and utilization.

With a greater awareness of this condition, many other cases will undoubtedly be reported. The long-term study of these patients might well prove informative in the investigation of the genesis of atherosclerosis.

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A COMMON TYPE OF VERTIGO RELIEVED BY TRACTION OF THE CERVICAL SPINE*

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THE purpose of this report is to call attention to a common form of vertigo that is generally unrecognized and often erroneously attributed to cerebral arteriosclerosis. As in true objective vertigo the patient complains that, with a sudden change in head position, objects begin to move, usually revolving clockwise or counter-clockwise. There is a sense of falling to one side, a need to hold on for support or to return to the original bodily position. The mechanism of this vertigo is not established, but clinical evidence is offered to show that it results from cervical nerve root irritation due to hypertrophic arthritis, or to traumatic or postural strain of the cervical spine. It is often associated with other manifestations of this spinal syndrome and responds in the same way to traction and exercises. It is not associated with the usual manifestations of intracranial disease or cerebrovascular insufficiency due to arteriosclerosis. There is no mental confusion, memory failure, or sensory or motor disturbance. The neurologic examination is negative. Tinnitus is absent and hearing unimpaired, in contrast to Ménière's syndrome, with functional or organic disturbances of the labyrinth.

Interest in this form of vertigo started in the course of studies on the dorsal spine syndrome with chest pain simulating that of coronary origin.^{1, 2, 3} In a reported group of 43 patients with chest pain as the chief complaint, a history of vertigo was elicited in 21. In some, this symptom had recurred over a period of years. Generally it was mild and transient, and was elicited only by questioning. On the other hand, in several it was severe and, at times, incapacitating.

The following case reports illustrate clinical aspects of the syndrome. The most striking feature was the precipitation of the attack by sudden turns of the head and neck from long-maintained positions, and almost regularly by the act of getting out of bed in the morning. The attacks of actual vertigo were usually of very short duration, lasting less than a minute and often only a few seconds, but they recurred frequently. After certain bodily activity, such as dressing or walking, the tendency to recur was lessened. An unsteadiness of gait persisted in most instances a few minutes, in some for hours, and a few were incapacitated for days. With the vertigo there were nausea and occasionally vomiting. In several instances attacks were reproduced by having the patient get up suddenly from the examining table. Most of these attacks were interrupted and recurrences prevented or lessened by cervical traction and exercises. The manual method in the reclining position and the overhead method of Hanflig were used.⁴

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CASE REPORTS

Case 1. A 60 year old minister was seen February 11, 1950, complaining of an attack of "dizziness" and nausea which had started in bed that morning as he turned from one side to the other. There seemed to be rotary movements of the room and he thought the bed was "turning upside down." When he tried to get out of bed the vertigo became more marked and nausea developed; with it there was mild epigastric distress. When he tried to stand he felt that he was falling to one side, and simultaneously he experienced pain in the suboccipital region. When he lay flat on his back the symptoms disappeared; when he moved from side to side in bed, or got up, they recurred. He gave a past history of low back pain of 20 years' duration. He had been using a large pillow and sleeping in a propped-up position.

When examined several hours after the onset he still complained of slight vertigo with sudden changes in head position, and moved about with caution. Neurologic examination was negative. There was no nystagmus. There were some spasm and tenderness of his posterior cervical muscles. Head rotation was not appreciably limited. Eye grounds were normal. There was no definite narrowing of the retinal arteries. Blood pressure was 150/80 mm. of Hg.

When manual traction was applied to his cervical spine, vertigo was immediately intensified and he began to vomit. Ten minutes later the vertigo and nausea subsided completely and did not recur. Bed boards, a small pillow and exercises were recommended. Overhead cervical traction was given on three occasions at weekly intervals.

Up to the present time, three years after the first severe attack, he has had a few mild and transient episodes of vertigo, never incapacitating and regularly relieved by the exercises.

Case 2. A 52 year old male short order cook was first seen February 10, 1951, complaining of two attacks of "dizziness" the previous day. One attack had occurred while making up an order: raising his head suddenly from a forward position, he had lost his balance and seemed to be falling in a "jerky manner" to one side. The room had seemed to rotate, and he could not stand without holding on to something. Five minutes later he became nauseated, and during the next hour transient bouts of vertigo recurred with changes in head position, forcing him to sit quietly to avoid head motion. A second attack occurred that evening after he had leaned forward for many minutes in a box seat at the theatre. When he suddenly straightened up, objects seemed to move and he became nauseated. Recurring vertigo continued after he got up, and his gait was unsteady until he got home an hour later. His past history was negative except for "curvature of the spine," because of which he had been excused from military service in 1942.

Neurologic examination was negative. There were no abnormalities of the mouth or tongue to suggest a vitamin deficiency. He showed flatness of the dorsal spine from D1 to D6. There was angulation in the region of the sixth dorsal vertebra, with lateral curvature to the right. Over the third to fifth dorsal spinous processes there was moderate tenderness but no referred pain. There was tenderness over the first right to third costochondral junctions. Eye grounds were normal. Blood pressure was 140/90 mm. of Hg.

While in the office he developed another attack of vertigo on suddenly getting up from a chair. Objects in the room seemed to rotate to the right. There was no nystagmus. He was helped to the examining table and given manual traction in a reclining position. Vertigo was immediately relieved. Ten minutes later, on getting up from the examining table, he developed another attack of vertigo which was instantly relieved by manual traction.

Exercises were recommended. When the patient was checked 14 months later, the attacks had not recurred.

Case 3. A 63 year old business executive was seen September 19, 1950, complaining of attacks of vertigo which had started 11 days before as he rolled out of bed in the morning. The back of his neck was stiff and sore and he felt as though something had hit him on the head. The room seemed to move around, objects rotating to the left. He was unsteady when he got to his feet, and became nauseated and vomited three times. Vertigo disappeared as soon as he lay flat on his bed but recurred the moment he raised his head. After he finally got on his feet and moved about the unsteadiness became progressively less marked during the next few hours, but later that day the vertigo recurred several times, always in relation to certain postures and sudden head movements. He then consulted an internist, who made a diagnosis of cerebral arteriosclerosis.

During the next two days the attacks became progressively less frequent, but six days later they recurred in intense form. Each morning severe vertigo made getting out of bed difficult. Certain movements, such as bending to tie his shoes or turning his head quickly from side to side, produced symptoms. Usually he could find one position that relieved or reduced the vertigo. His past history revealed a lumbar disc condition since 1943, with periodic low back pain sometimes radiating down his right leg.

Examination showed slight limitation of neck rotation in both directions. There was no muscle spasm. There was acute tenderness but no referred pain over the fourth, fifth and twelfth dorsal vertebrae, and tenderness at the first and second left costochondral junctions. Physical and neurologic examinations were otherwise negative. He was alert, his memory was excellent and his hearing was normal. There had been no mental confusion or sensory or motor disturbance at any time. The eye grounds were not remarkable. Blood pressure was 170/90 mm. of Hg. Roentgen examination of the cervical and dorsal spine showed spur formation about the anterior margins of the borders of the fifth and sixth cervical vertebrae, and narrowing of the fifth and sixth intervertebral discs. The lateral projection of the spine was practically straight.

He was given a course of overhead traction and exercises, with striking reduction of symptoms. When last examined, May 11, 1951, he stated that he had had a few mild bouts of vertigo, usually in periods when he had neglected his program of exercises.

Case 4. A 44 year old male business executive was first examined August 18, 1950. He complained of a severe attack of dizziness that had started the previous morning as he walked from his house to his car: "The sidewalk began to spin." He staggered as if drunk, and a neighbor had to help him back. Unsteadiness of gait persisted for several hours, any sudden change in position seeming to produce rotary movements of his surroundings. At least once or twice a month for several years he had had similar episodes of vertigo, but of only a few seconds' duration, most often on getting out of bed and occasionally on stooping or getting up from a stooped position. He gave a history of low back pain since the age of 23.

Physical examination showed kyphosis of the dorsal spine, with angulation in the region of the first and second dorsal vertebrae. There were slight limitation of head rotation to the right and moderate costochondral tenderness over the first and second left junctions. There was no dorsal spine tenderness. The neurologic examination was negative. Eye grounds were normal. Blood pressure was 130/85 mm. of Hg.

On getting up from the examining table the patient developed a typical attack of vertigo. For a few seconds there was a lateral nystagmus. He had a feeling of insecurity as he sat up, held onto the table with both hands and then insisted on reclining. After resting for five minutes he got up suddenly and again precipitated vertigo. This was repeated twice and each time vertigo was induced. Manual traction was then applied for a few minutes. Thereafter he got up from the table without

symptoms. The same procedure was repeated, again without the recurrence of vertigo.

When seen three weeks later the patient reported that mild bouts of vertigo had recurred on four occasions as he was getting out of bed and twice as he was going down stairs. He went through the performance of getting up from the table three times without developing symptoms. Physical and neurologic examinations were negative.

In May, 1951, nine months later, he wrote that attacks of vertigo had not recurred since his examination in September and that he had kept to the program of exercises.

Case 5. A 56 year old business man was first examined September 10, 1950. That morning as he got up the entire room had seemed to move around to the right. He got back into bed quickly. When he tried to get up again a few minutes later, vertigo recurred, this time with nausea. With difficulty, by holding onto the walls, he got to the bathroom, but the vertigo and nausea persisted until he returned to bed. They recurred 10 minutes later when he tried again to get up. After a fourth try, vertigo was less marked and gradually disappeared. For the past two years he had had similar attacks on getting out of bed or on getting up suddenly from a stooped position. These attacks, however, were never severe. Five years earlier he had developed pain of sciatic nerve distribution due to a lumbar disc dislocation. This condition, although somewhat improved in recent months, was still causing pain. All movements of his trunk had to be slow and cautious. In addition, he complained of attacks of suboccipital headache of two years' duration. These attacks usually began at 5 a.m., increasing in severity until he got out of bed approximately two hours later. After he was up and about they decreased in severity, and had usually disappeared by 10 a.m.

The physical examination showed moderate limitation of neck rotation on both sides, and spasm and tenderness of the deep cervical muscles posteriorly. There was no costochondral tenderness. Eye grounds were not examined. There was no nystagmus. Blood pressure was 140/85 mm. of Hg.

When examined he was still unsteady in gait and feared recurrence of vertigo. He was given manual traction, and exercises and a change to a small pillow were recommended. During the next few days vertigo and suboccipital headache were remarkably lessened. He was particularly impressed with the relief from suboccipital headache. During the next few months he had a few mild episodes of vertigo. He had not carried out exercises as recommended, but volunteered that when he did they seemed to prevent attacks.

Case 6. A 70 year old dentist was seen eight years ago for an attack of chest pain that proved to be of spinal nerve root origin. At that time he also gave a history of transient episodes of vertigo of 10 years' duration. When seen a year later (May 9, 1946), his chief complaint was incapacitating attacks of dizziness of four days' duration. The first episode had come on while he reclined on a couch in his office. The room had seemed to rotate in a clockwise manner, and he had to hold on for support. Upon getting up he noted that vertigo was less marked, and that standing erect with his head back gave him relief. Such attacks recurred several times during the next four days. At times he walked "as though drunk." Physical examination was not remarkable except for an unsteady gait and tenderness in the region of the seventh cervical vertebra. Cranial nerves were normal. There was no nystagmus, cerebellar or posterior column ataxia or abnormal reflexes. His eye grounds showed slight narrowing of the retinal arteries. When pressure was applied over the sixth spinous process he noted that the room became steady. He got up and walked about and found that vertigo had ceased. Exercises were recommended and vertigo did not recur for several months.

On December 13, 1946, he complained again of an attack of vertigo of two hours'

duration. While working on a patient he felt that the room was beginning to spin in a clockwise direction, and was forced to hold on for support. Reclining on his couch aggravated the condition. There was slight nausea. Rotating his head from side to side decreased the vertigo, and it was somewhat relieved when he stood erect with back and head to the wall. Rotary movement of objects seemed to persist for half an hour, after which he was conscious only of unsteadiness in gait and nausea. When seen two hours after onset, he walked slowly and with caution, and complained of nausea. Neurologic and physical examination was negative except for spasm of posterior cervical muscles, limitation of head rotation to the right, and marked tenderness in the region of the second and third right costochondral junctions. After manual traction in a reclining position his unsteady gait disappeared. Nausea, however, was unchanged, and one hour later he vomited. Once that night he got up and noted that some vertigo had returned. The next morning he was entirely free of vertigo and nausea but noted soreness in the back of his neck.

Roentgen examination of the spine showed anterior and posterior osteophytes of advanced degree over the fourth through the seventh cervical vertebrae. There was narrowing of the discs between the fifth and sixth intervertebral joints. There were scoliosis to the left and marked straightening of the cervical spine. The dorsal spine showed advanced changes over the anterior margins of D3 to D9.

Four years later (February 14, 1951), he was seen for a third severe attack of vertigo. This attack, too, was immediately terminated by traction, and he was essentially free of symptoms until July 23, 1951. At this time he again complained of transient episodes of vertigo and of unsteadiness in gait of four days' duration. During these attacks he noted that the room seemed to move to the right and that he had a tendency to fall to the left. Rotary movements were absent. There was nausea. Reclining on his office couch and certain movements of the neck and head definitely aggravated the symptoms. Overhead traction brought immediate and complete relief. He returned to work that same morning and to date has had no recurrences.

Case 7. A 38 year old shipping clerk and former U. S. Marine was examined February 24, 1951. He complained of upper right chest pain, vertigo and occipital headache of four months' duration. All symptoms appeared after an automobile accident in which he received direct injury to his right shoulder and side of the neck. Shoulder and neck pain subsided during the first few days after the accident, but at this time he began to complain of upper right chest pain, which was worse after prolonged sitting, or in the course of turning from side to side in bed. It also occurred after stooping, coughing, sneezing or straining at stool. A chest plate taken at this time was negative. During the next few days he noted neck stiffness and vertigo, particularly in the morning. As he got out of bed the room seemed to rotate, and he was obliged to sit down and hold on for support. These attacks, occurring daily, subsided within a minute but recurred once or twice before he finished dressing. Occasionally suboccipital headache was also noted in the morning, but this usually disappeared by the time he had left the house.

Physical examination showed a marked dorsal spine kyphosis. The region of D1 to D6 was abnormally flat. There was tenderness over the entire cervical and dorsal spine and anteriorly over the first to seventh right and second left costochondral rib junctions. Head rotation was markedly limited to the right. There were tenderness and spasm of the posterior cervical muscles. Blood pressure was 135/90 mm. of Hg.

During the next two months he was given a program of exercises and overhead traction treatments, with striking improvement in all symptoms. Within a few days vertigo did not recur as before, and chest pain was greatly reduced. Four weeks after the program was started there was some return of vertigo. Traction and exercises again had an immediate beneficial effect. Since then vertigo has not recurred.

DISCUSSION

In the literature on cervical radiculitis which is meager, references to vertigo are rare. Kelly⁵ noted that vertigo and suboccipital headache were less commonly recognized manifestations of this condition. Symposia and papers on the general subject of vertigo do not mention this form. It is recognized that bouts of vertigo may be the first manifestation of a cerebral lesion such as thrombosis, hemorrhage, aneurysm or neoplasm, and that such attacks may occur hours or days before localizing signs appear. This circumstance is probably responsible for the currently accepted view that cerebral arteriosclerosis, *per se*, will account for this symptom. There are no data in the literature to support this concept. It was interesting to note in a recent review of the neurologic aspect of vertigo that arteriosclerosis was not listed among other specific causes.⁶ In my experience vertigo is not a particularly common symptom in the aged who have progressive loss of memory or mental deterioration presumably due to advanced cerebral arteriosclerosis. Nor can it be attributed to postural hypertension or the carotid sinus syndrome which most often causes a faintness or unconsciousness rather than true vertigo. Six of these patients, carefully examined for evidence of an irritable carotid sinus, showed a normal response in every instance.

Table 1 summarizes the clinical findings in 20 patients, with one exception seen over a period of two years for vertigo as a major complaint. Nine were age 60 or over, and the age in 11 varied from 38 to 56. Symptoms had been present for years in eight, and for periods of seven to 16 years in four. Blood pressures were normal in 11, slightly elevated in eight and moderately elevated in one. It is recognized that hypertension is associated with an increase in arteriosclerosis, but it has also been shown that this type of vertigo is not a common symptom of hypertension.⁷

The underlying pathology and mechanism of this condition, while not established, are suggestive. Spector's analysis of the neuroanatomic systems underlying vertigo shows how cord disturbances may play a rôle in its production.⁸ The awareness of one's body in space is based on a correlation of impulses coming from the eye, ear and proprioceptive organs of the neck, trunk and extremities. The medial longitudinal bundle extends into the cord and coordinates the vestibular apparatus with the eye and the anterior horn cells of the spinal cord. Nerve root pressure, setting up a bombardment of afferent impulses to the cervical cord, could understandably disturb this primary coordinating system and cause vertigo. It was of interest that nystagmus, usually present when there is intracranial irritation of the medial longitudinal bundle, was not observed in several patients immediately after transient attacks or during periods when there was nausea and the gait remained unsteady.

Although vertigo was the chief complaint, other manifestations of the cervicodorsal spine syndrome were often present: suboccipital headache,

TABLE I
Clinical Data in 20 Patients with Vertigo

Case numbers	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Age and Sex	M. 60	M. 52	M. 63	M. 44	M. 56	M. 70	M. 38	F. 52	M. 36	F. 69	M. 67	F. 41	F. 55	M. 76	M. 60	F. 71	M. 85	F. 62	M. 51	M. 47
Duration of Vertigo	Hrs.	1 Day	Hrs.	Vrs.	2 Vrs.	10 Vrs.	4 Mos.	4 Wks.	7 Vrs.	1 Wk.	Wks.	10 Vrs.	2 Vrs.	10 Days	2 Vrs.	16 Vrs.	1 Wk.	2 Mos.	3 Wks.	2 Days
Morning attacks	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rotary movement of objects; relation to position	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nausea	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+
Nystagmus, tinnitus, memory changes	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+
Unsteady gait following attacks	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
Attacks reproduced under observation	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
Good immediate response to traction	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Good late results to treatment	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Symptoms temporarily increased by traction	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Suboccipital headache	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
History of shoulder girdle or chest pain	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
History of low back pain	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Limitation of head rotation	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tenderness over cervical or dorsal spine	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Costochondral tenderness	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Average Blood Pressure	150/80	140/90	170/90	130/85	130/80	160/90	155/90	160/90	170/90	200/110	190/100	120/70	158/90	190/90	110/75	210/100	180/100	210/90	110/70	160/85

shoulder girdle and chest pain, limitation of head rotation, spasm and tenderness of the posterior cervical muscles, and tenderness over the cervical or dorsal spine and in the parasternal region. In several cases, roentgen examination of the cervical spine showed advanced changes, with spur formation, narrowing of the intervertebral discs and straightening or reduced curvature of the spine. Many also gave a history of low back pain, lumbar disc dislocation and abnormal curvatures which usually result in readjustments and strain in the upper region of the spine.

The radicular distribution of changes in skin sensation in patients with shoulder girdle and chest pain in this condition suggests nerve root involvement, and a similar upper cervical mechanism is assumed as the basis for vertigo. In most instances hypertrophic arthritis or postural strain or both are present. In some, symptoms follow local injury caused by a sudden jolt to the head or shoulder girdle, or an unaccustomed physical effort with torsion on the cervical spine and its structure. Disc injuries with displacement, so common in the lumbar region, may also occur in the cervical spine and account for this syndrome. Case 7 illustrates the occurrence of pain and vertigo following direct injury to the shoulder girdle and cervical spine.

Just how traction and exercises operate to relieve symptoms is not clear. That an immediate effect on root irritation is produced by traction can be demonstrated by its effect on parasternal tenderness. This tenderness in the region of the costochondral junctions, invariably present in the dorsal spine syndrome, is often immediately relieved or abolished while traction is applied.⁹ This again would suggest some variable irritating mechanical factor. If we assume a similar mechanism as a basis for vertigo, the beneficial effect of traction and exercises is explained. It is also to be expected that at times symptoms will be increased by these procedures. Vertigo and nausea were temporarily aggravated and vomiting induced in four patients. Although traction relieves vertigo and for a time may prevent recurrences, it does not permanently alter the underlying condition responsible for the development of this syndrome. The importance of postural correction, a low pillow under the head during sleep and the continuation of daily exercises should be emphasized.

It is appreciated that the response to therapy in itself is not always conclusive. When only a few attacks have occurred, their disappearance could be attributed to spontaneous improvement and not to therapy. On the other hand, the response in some patients was so dramatic that a relationship could not be doubted. Patient R. S. (case 10, table 1), for example, had had persistent vertigo for seven days and was so totally incapacitated that in every move out of bed she had to be assisted. When seen she could not walk or stand without support. There was constant nausea, and rotary movements of the room seemed to occur while she sat in a chair. Initial traction increased nausea and induced vomiting, but vertigo was decidedly diminished. Traction was then continued intermittently for one hour. When she left

the office a little later she was able to walk unassisted down a flight of stairs. During the next 24 hours she complained of headache and considerable jaw pain, but vertigo did not recur. Two days later she was up and around and returned to household activities, and up to the present symptoms have not returned.

The significant clinical feature is not only that vertigo is precipitated by sudden changes in position but also that it follows a prolonged incorrect head posture and is usually less marked or disappears when the patient becomes active. Attacks occurred most often in the morning, after hours of ante-flexion of the head on a large pillow, or after a prolonged bent-forward position, as in the case of the short order cook (case 2) or the dentist (case 6).

Evidence that this vertigo is of cervical origin may be summarized as follows: (1) The striking response to traction and exercises, as shown by the immediate effect on the attack itself and the prevention of recurrences. (2) The close relation of the attacks to a prolonged position of the cervical spine, the effect of sudden changes from this position, and the reduction of attacks after bodily activity has been resumed. (3) The high incidence of the other manifestations of the cervicodorsal radiculitis. (4) The absence of clinical manifestations of intracranial disease, cerebral arteriosclerosis and disturbances of the labyrinth.

CONCLUSION

1. Evidence is presented to show that a common form of vertigo, heretofore attributed to cerebral arteriosclerosis, is of cervical nerve root origin.
2. This vertigo is effectively treated by appropriate orthopedic measures.

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SPLENECTOMY IN RHEUMATOID ARTHRITIS *

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THE purpose of this paper is to suggest a new cause and effect for the beneficial sequelae produced by splenectomy in Felty's syndrome. Felty¹ described a syndrome of mild rheumatoid arthritis associated with fever, secondary anemia (in four of five cases reported), leukopenia ranging from 1,000 to 4,200 leukocytes, splenomegaly and tachycardia. Rheumatologists are practically unanimous in believing that this syndrome is a variant of rheumatoid arthritis.

Forty-six papers¹⁻⁴⁶ have been published on the value of splenectomy in rheumatoid arthritis; 37 patients have been described in these papers as having undergone splenectomy successfully. The effects of splenectomy in these cases may be divided into two components: the first effect is one concerning hematopoiesis, the second the antirheumatic action. Splenectomy was first attempted in patients with rheumatoid arthritis who showed evidence of leukopenia with or without thrombocytopenia and secondary anemia and splenomegaly. Bach and Jacobs⁴⁶ omitted discussion of the hematopoietic effect resulting from splenectomy in rheumatoid arthritis, and discussed the antirheumatic effect in 12 patients suffering from rheumatoid arthritis from whom the spleen had been removed some time during the previous year.

HEMATOPOIETIC FACTOR

Wiseman and Doan,⁴⁷ Dameshek and Estren⁴⁸ and Steinberg⁴⁹ have explained why the blood picture returns to normal in cases of hypersplenism. Wiseman and Doan gave evidence that the spleen in three patients with hypersplenism showed extreme plasmacytosis with excessive phagocytosis of the granulocytes. Dameshek maintains that one of the normal functions of the spleen is to exert an inhibitory effect on the bone marrow, and that this may become increased when splenomegaly occurs. Thus he states: "accentuation of this normal function is termed 'hypersplenism' and manifests itself in increased hemolytic activity, in inhibition of hematopoiesis or by 'blocking' the escape of mature cells from the bone marrow. In the two latter instances various blood cytopenias result." Steinberg noted a hyperplastic marrow in Felty's syndrome, and a pancytopenia or leukopenia in rheumatoid arthritis associated with splenomegaly. This decrease in blood cells was noticed only in the peripheral blood. He was therefore of the opinion that the spleen acted in some way or other as a barrier between the overactive bone marrow and the cytopenic peripheral blood. Neither Wiseman and Doan nor Steinberg noted inhibition of the bone marrow itself in their cases, which is in disagreement with Dameshek's opinion. Hirsch-

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boeck⁸⁰ was able to observe phagocytosis or granulocytosis in the spleen of these cases, although in one case he was able to show a white cell count of 11,700 in the splenic artery against a white count of 2,600 in the splenic vein. These various disagreements have stimulated the author to reevaluate this subject.

Investigations in both animals and human beings shed some light and indicate that, while hypophysectomy results in atrophy of the spleen, splenectomy results in hypertrophy of the anterior pituitary gland. Perla⁴⁹ found:

- 1) Removal of the pituitary in the adult rat resulted in progressive atrophy in the spleen. The ratio of spleen weight to body weight at the end of two months' observation was exactly one-half of normal.

- 2) Hypophysectomy completely inhibited regeneration of splenic tissue after partial splenectomy.

- 3) The daily administration of an anterior pituitary emulsion of cattle to rats over a 10 day period resulted in hypertrophy of the spleen to twice normal size. This hypertrophy of the spleen was due primarily to marked hyperplasia of the reticular and endothelial cells of the red pulp. There was also some increase in the size of the follicles. That there was a specific factor present in the anterior pituitary regarding the spleen was evidenced by the fact that an alkaline extract would stimulate hypertrophy of the spleen, but an acid extract would have no such effect. The acid extracts contained both thyrotropic and adrenotropic factors.

Friedgood⁸¹ injected an alkaline extract of the anterior pituitary daily into 73 adult male and female guinea pigs. He also found that hypertrophy of the spleen occurred with such medication. Smith⁸² first reported in 1930 that atrophy of the spleen and lymphoid tissues, along with other endocrine or target glands, was a sequel to hypophysectomy in the rat. Houssay⁸³ found that the Malpighian corpuscles were more numerous and larger in the hypophysectomized dogs than in the controls. Also, the Malpighian corpuscles in hypophysectomized puppies were more numerous than normal, but not larger. In the animal, at least, there seems to be a definite relationship between the anterior pituitary gland and the spleen.

Waugh⁸⁴ reported on the autopsy of a patient whose spleen was removed on August 15, 1925, for essential thrombocytopenia, and who died March, 1929, of acquired hemolytic jaundice. The most interesting finding was the abnormal pituitary gland, which was twice normal size due to hyperplasia of the anterior lobe. This consisted of an increase in the chromophobe cells, with an extreme extension into the pars posterior. Other evidence of hypercortisonism induced by this enlargement of the anterior pituitary gland was the increase in hair on the limbs. Thus, inadvertently, there is confirmatory evidence that not only does the anterior lobe of the pituitary gland hypertrophy in animals who have been splenectomized, but a similar event also occurs in the human individual. Further study of the pituitary gland of human beings who have been previously splenectomized will be

required before this relationship can be accepted as a fact. However, the material to date would indicate that this relationship of the anterior pituitary and the spleen is no mere accidental occurrence.

Barcroft and Stevens²⁶ noted that the spleen contracted in pregnant dogs. They found that the contraction during heat and pregnancy was neurogenic in origin, since this contraction could be abolished by denervation. However, the contraction of the spleen associated with lactation was humoral in origin, since the dissociation was not possible by denervation. They advanced the theory that the spleen contracted during pregnancy to supply more blood to the uterine vessels and also to aid in fetal hematopoiesis.

Following are three case histories of rheumatoid arthritis associated with splenomegaly (splenectomized):

CASE REPORTS

Case 1. A 46 years old white female was first seen 12 years ago, at which time she had complained of painful, swollen, stiff joints of two years' duration. In rapid succession practically all the joints of her body had become involved. Various methods of therapy had been employed but with the same result, a progressive downward course. Physical examination revealed a poorly developed, undernourished, ill-appearing white female 5 feet 3½ inches tall, whose nude weight was 108½ pounds (standard weight, 132 pounds); temperature, 97.4° F.; pulse, 94; blood pressure, 110/80 mm. of Hg. Her face was deviated to the right by a paralysis of the left facial nerve as result of removal of a nonmalignant parotid tumor in 1936. The teeth appeared grossly innocent. Her posterior pharynx was not visible because she could not open her jaws as result of involvement of the mandibular joints with arthritis. A thyroid scar was present; a thyroidectomy had been done in 1926. Examination of the lungs, heart and abdomen was negative. Vaginal examination was negative; the cervix appeared healthy. The proximal interphalangeal joints had fusiform swelling. Wrists, ankles and knees were hot and swollen; the wrists had practically no motion. A 90° angle deformity of the left elbow was present. Pronation and supination were absent in both elbows. The right knee had a 10° flexion deformity.

Laboratory Examination: Urinalysis, negative; red blood cells, 4,300,000; hemoglobin 10 gm.; white blood cells, 6,500. Differential: Stabs, 11; segs. 50; lymphocytes, 20; monocytes, 11. The sedimentation rate was elevated at 0.80 (normal, 0.08 to 0.35). Agglutination for *Brucella abortus* was negative.

Orthopedic examination on June 23, 1939, revealed no demonstrable activity of the arthritic process in the hips or ankles. The increased local heat in the knee joints had disappeared, but there was marked thickening of the synovial tissue of both knee joints. A 90° contracture of both elbows and a flexion contracture of the left wrist of about 45° were present. There was about 10° limitation of extension in both knees.

The patient was observed frequently until August 2, 1940. The white blood count varied between 6,350 and 8,450 during this period, the hemoglobin from 10 gm. to 12.4 gm. Rest, daily warm baths with active and passive exercises and massage resulted in very little improvement, and the patient was not seen again for a long period.

Her next period of observation was during her admittance to the Rochester General Hospital on August 5, 1951, at which time she was 46 years of age. She was admitted for evaluation and treatment of flexion deformities of her knees; she had been unable to walk for the past 10 years because of contractures of her knees. The

positive findings were restricted to her joints. There was marked atrophy of the muscles of the entire body, particularly notable in the upper and lower extremities. Practically all the joints of her body had become involved with rheumatoid arthritis. There were complete ankylosis and flexion of both wrists. Marked flexion deformities were present in the elbows. Forty-five degree flexion deformities were present in the knees, which had only about 15° motion. Dorsal kyphosis was present in the spine. Lateral motion of the neck to the left was not possible, and to the right was restricted to 45°.

Hospital Course: The patient was placed on Buck's extension, and after two weeks there was slight improvement in extension of both knees. A posterior cap-

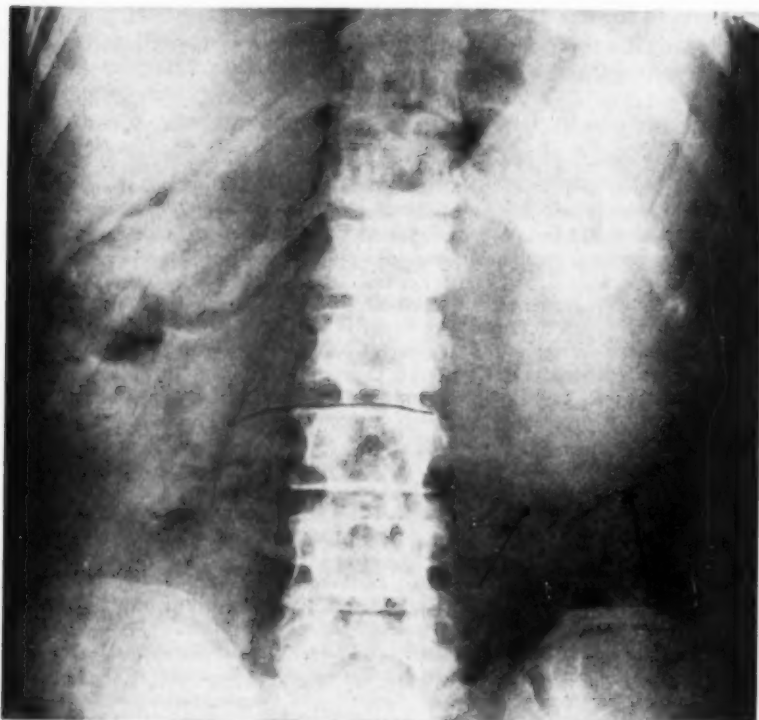


FIG. 1. Case 1. Flat plate of abdomen showing large spleen. Splenomegaly may often be detected by radiograph.

sulotomy was done on the left knee on August 25. She developed an elevated temperature postoperatively which continued for 13 days; the highest temperature spike was 104° F. Râles developed in both bases. She was treated with penicillin and intravenous aureomycin. The temperature returned to normal the thirteenth day postoperatively. However, the capsulotomy failed to heal. On September 30 a diagnosis of Felty's syndrome was made based on the findings of rheumatoid arthritis, an enlarged spleen, marked leukopenia, iron deficiency anemia and normal bone marrow findings. Figure 1 shows the large spleen by radiograph.

The various blood studies before and after splenectomy are shown in the following table:

TABLE I

Case 1

Date	RBC	Hb.	WBC	Platelet	Stab	Seg.	Lymph.	Mono.	Eos.	Bas.	Sed. Rate
5/ 3/50	4,680,000	13	2,700	240,000	11	16	45	26	1	1	17
8/ 6/51	4,020,000	12.1	2,800		14	24	50	12			57
8/31/51	3,550,000	10	5,200								
9/19/51		10	2,600		12	24	44	18	1	1	35
9/26/51	Normal marrow (Fig. 6)										
10/18/51			2,400		14	26	48	12			
10/23/51			4,100	120,000							8:50 a.m.
10/23/51			2,400	150,000	14	30	42	14			9:00 a.m.
10/23/51			9,100	122,000		12	75	12			9:10 a.m.
10/23/51			5,600	150,000	8	20	60	11	1		9:20 a.m.
10/23/51			5,300	160,000	4	18	62	15		1	9:30 a.m.
10/23/51			3,000	170,000	8	16	60	16			9:45 a.m.
10/26/51	Bleeding time, 2½ minutes; clotting time, 1 minute.										
9/28/51	Own consultation—Feltz's.										
10/30/51	Splenic aspiration—smear of splenic aspiration = many erythrocytes, moderate number of lymphocytes scattered about. Occasional large reticular cell seen. Normal appearance.										
11/ 5/51	4,580,000	13.6	2,750	58,000	6	26	62	6			
11/ 5/51	Nonprotein nitrogen, 34; chlorides, 543; serum albumin, 3.1; serum globulin, 4.0.										
11/ 6/51	SPLENECTOMY										
11/ 6/51				148,000							
11/ 7/51	5,640,000	15.9	14,300	160,000	40	44	9	7			
11/ 8/51	5,220,000	15.1	14,900	140,000	8	59	14	19			
11/ 9/51	5,390,000	15.9	20,400	260,000	8	65	11	16			
11/10/51	Joint pains gone.										
11/10/51			11,300	480,000							
11/13/51			9,500	500,000							
11/14/51			11,000	580,000							
11/15/51			12,300	660,000							
11/16/51			9,400	710,000							
11/17/51			11,300	730,000							
11/19/51			8,800	740,000							
11/20/51			12,100	690,000							
11/24/51			6,300	440,000							
11/30/51			5,100	240,000							
12/ 1/51	5,080,000	14.5	7,100								
12/ 3/51			6,300	300,000							
12/ 6/51			9,200	310,000							
12/12/51	Bleeding time, 1 minute; clotting time, 4 minutes.										
12/15/51	4,580,000	13.3	5,100								
12/17/51			11,100	190,000							
12/20/51			12,300	280,000							
12/26/51			7,100	460,000							
12/29/51	4,420,000	13.8	8,600		4	29	65	2			4.4
1/ 2/52			9,800	240,000							
1/ 7/52			10,300	260,000							
1/10/52			9,900	240,000							
1/17/52			8,200	280,000							

The spleen (figure 2) removed November 6, 1951, weighed 670 gm. and measured 20 by 10 by 6 cm.; an accessory spleen 2 cm. in diameter was also removed. The capsules of both the spleen and the accessory spleen were smooth. The cut surface was firm (figure 3). The Malpighian corpuscles were very prominent and were widely separated by firm, red-brown pulp.

Microscopic examination of the spleen showed the Malpighian corpuscles to be very large, with prominent germinal centers (figure 4). The sinuses were markedly congested. The sinuses gaped and showed rather stiff walls where the erythrocytes had fallen out (figure 5). Trichrome stain showed a moderate increase in the fibrous

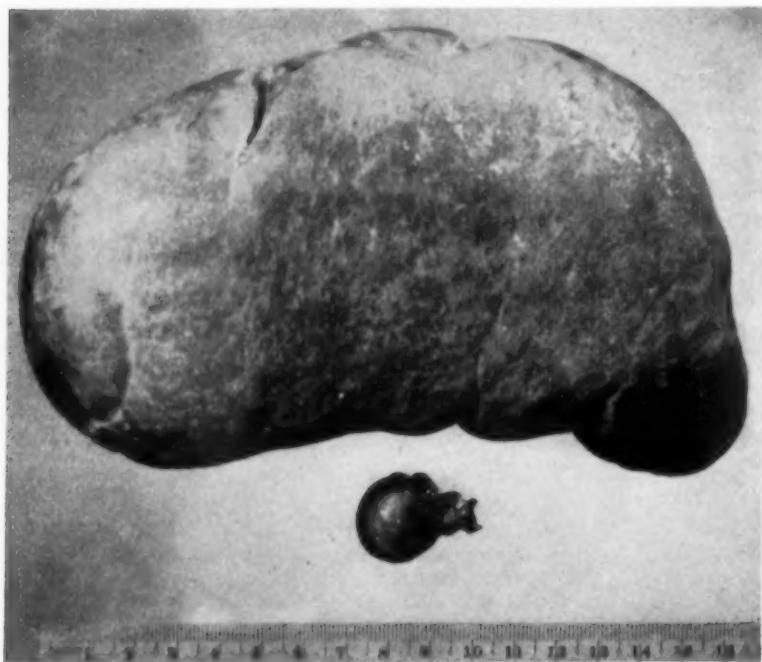


FIG. 2. Case 1. Large spleen, weighing 670 gm., removed at operation. Note accessory spleen. Failure of successful clinical response may occur if accessory splenic tissue is not removed.

tissue as well as in the red pulp in some of the germinal centers. The arteries were normal, without hyaline thickening. A conspicuous scattering of plasma cells was noticed in small groups or nests in the red pulp, as well as perivascular infiltration surrounding the trabeculae. No myeloid metaplasia was noted.

Diagnosis: (1) Congestive splenomegaly, moderate. (2) Plasma cell infiltration of the spleen, moderate.

The most interesting postoperative findings were the markedly improved relief of joint symptoms and the increase in range of motion of the small joints of the hands, wrists, elbows and shoulders. The relief of joint symptoms began approximately 24 hours after operation and has been maintained until the date of writing.

Case 2. A 38 year old white married female was first seen April 29, 1951, complaining of painful swollen joints of six months' duration. Her family physician had noted that she had an enlarged spleen and a white blood count of 2,000.

Examination revealed a well developed, well nourished white female, 5 feet 6 inches tall, whose nude weight was 161 pounds (standard weight, 142 pounds); temperature, 98° F.; pulse, 88; blood pressure, 130/80 mm. of Hg. She had an acneiform rash on her face. The pupils reacted to light and accommodation. Many teeth were missing; recent dental x-rays were negative. The tonsils had been removed; the posterior pharynx appeared innocent. Examination of neck, lungs, heart and abdomen was negative. It was interesting that abdominal examination failed to reveal definite enlargement of the spleen, despite her report that an abdominal film showed an enlarged spleen (figure 8). It was possible that the spleen was enlarged along

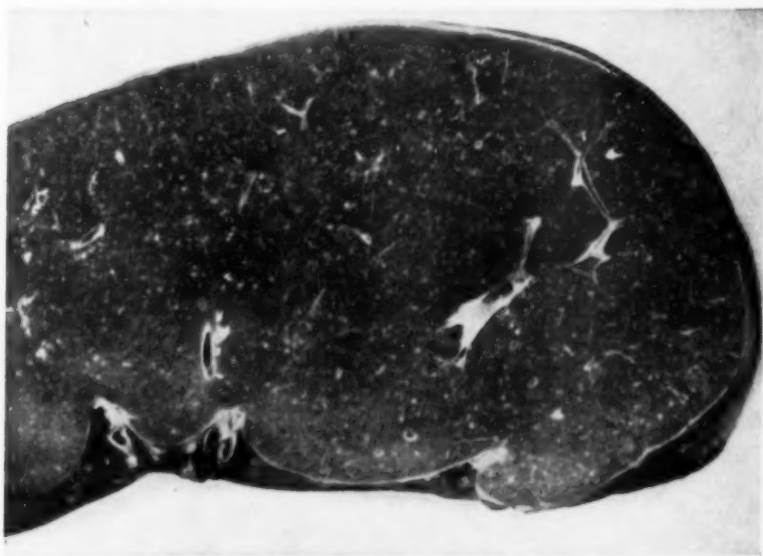


FIG. 3. *Case 1.* Cut section of spleen removed at operation.

the posterior aspect. The liver was not felt. The uterus was retroverted. Rectal examination was negative. There was slight swelling of the distal finger joints and definite swelling of all the metacarpophalangeal joints and both wrist joints. There was swelling of the left knee. All of these joints had painful motion. Motion of both shoulders was painful. There was tenderness of all the metatarsophalangeal joints. No enlarged lymph glands were felt. The deep reflexes were equal and active, and the vibratory sense was intact.

Urinalysis was negative; red blood cells, 4,560,000; hemoglobin, 13 gm.; white blood cells, 2,400. Differential: Stabs, 3; segs., 60, lymphocytes, 37. The platelet count was somewhat depressed at 265,000. The sedimentation rate was normal at 4 mm. per hour. The blood uric acid was normal at 2 mg. per cent. Serum albumin and serum globulin were both normal at 4.5 gm. and 2.9 gm., respectively. Throat culture revealed no pathogenic organisms. Bone marrow aspiration revealed no

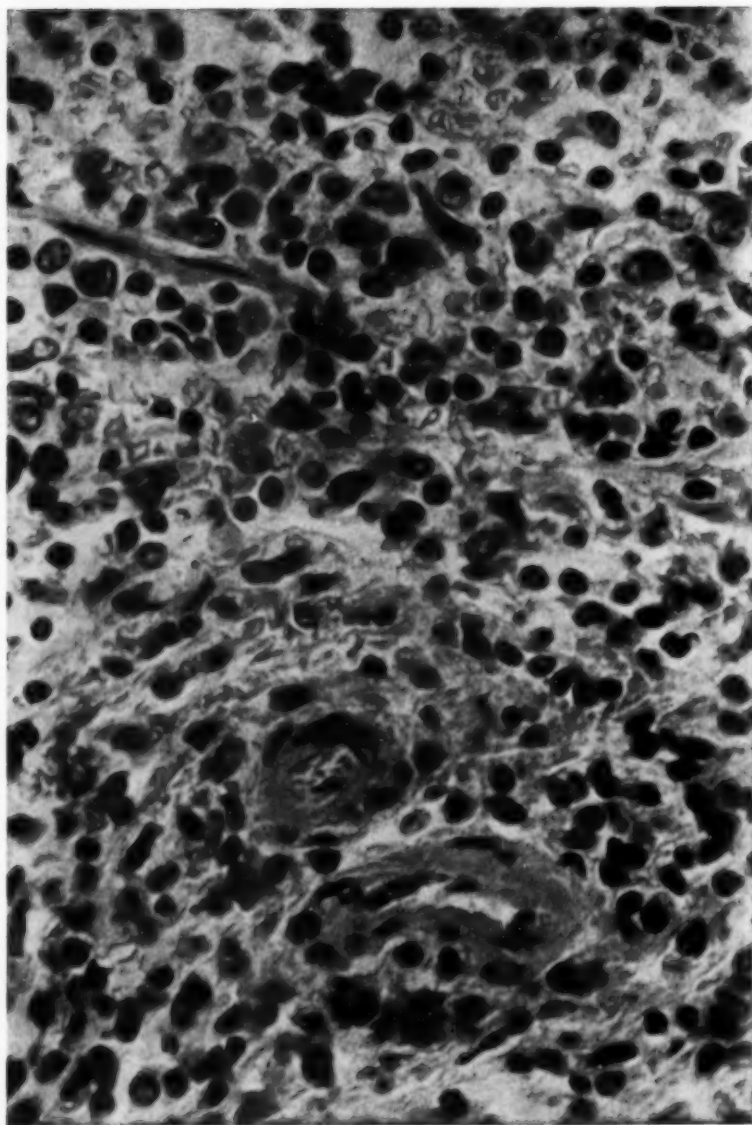


FIG. 4. Case 1. Microscopic section of spleen showing Malpighian corpuscle with prominent germinal center. Arteriole entering the germinal center.

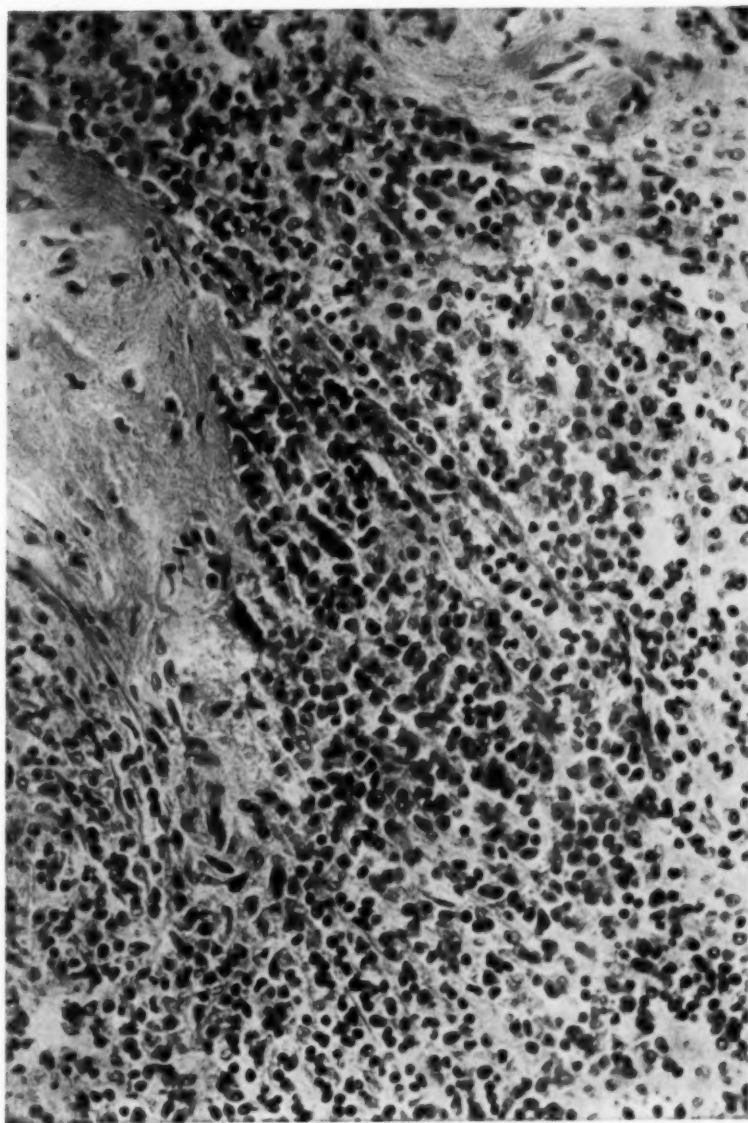


FIG. 5. *Case 1.* Microscopic section of spleen showing rather stiff wall of sinus where the erythrocytes have fallen out.

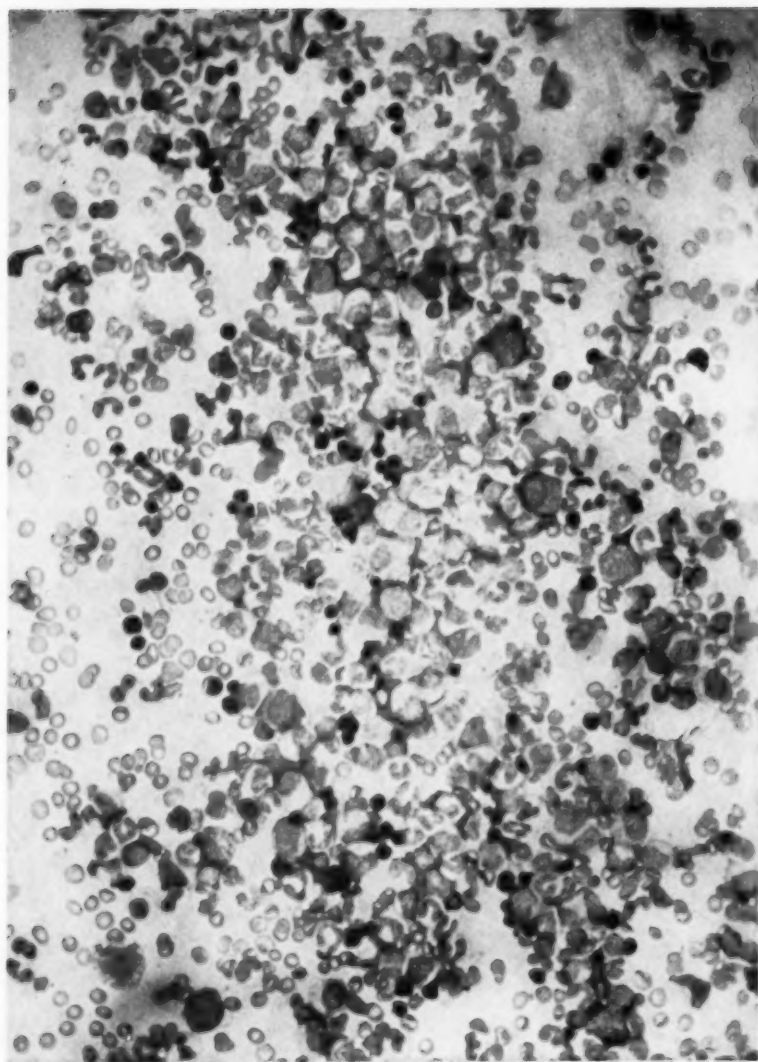


FIG. 6. *Case 1.* Normal bone marrow before splenectomy, September 26, 1951.

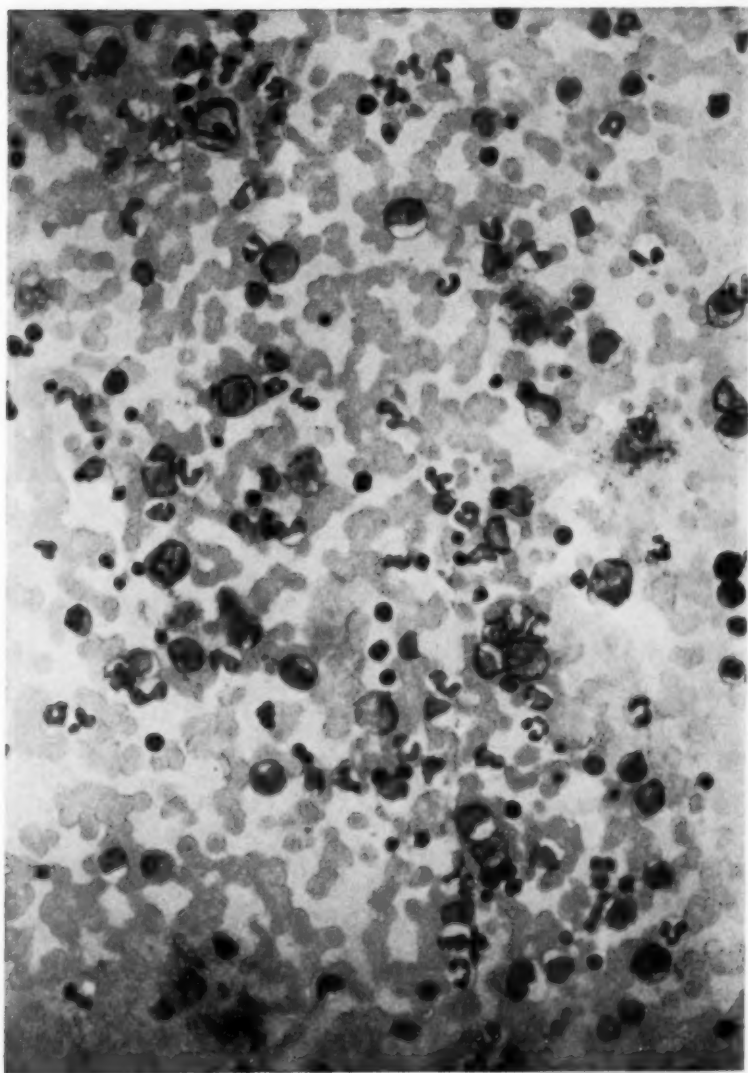


FIG. 7. Case 2. Normal bone marrow before splenectomy.



FIG. 8. *Case 2.* Large spleen detected by radiograph. Spleen could not be palpated.

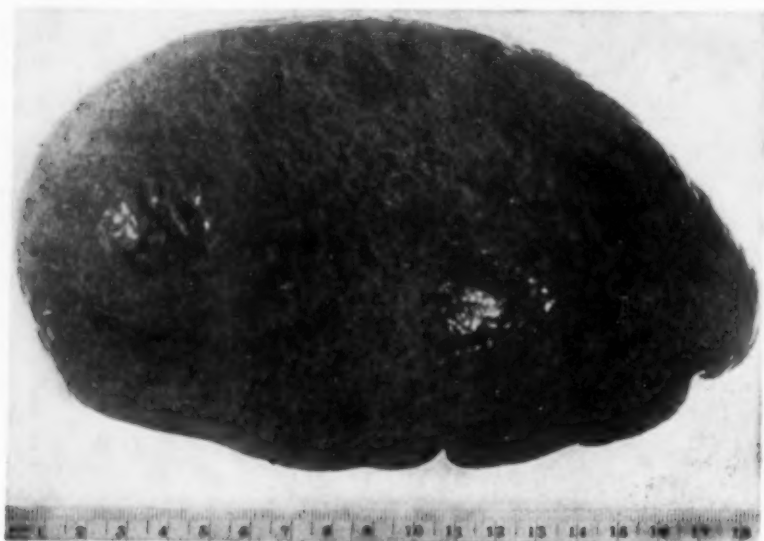


FIG. 9. *Case 2.* Gross specimen of spleen, weighing 850 gm., removed at operation.

evidence of Hargraves' cells of disseminated lupus erythematosus. No abnormal cell elements were present to suggest leukemia (figure 7).

Diagnosis: Felty's syndrome or disease.

X-ray examination of the abdomen on April 10 (figure 8), showed the enlarged spleen.

A splenectomy was performed at the Rochester General Hospital May 4, 1951. The spleen (figure 9) was uniformly enlarged, measured 20.5 by 12.5 by 6 cm. and weighed 850 gm. It was interesting that 560 gm. of blood had run off the spleen

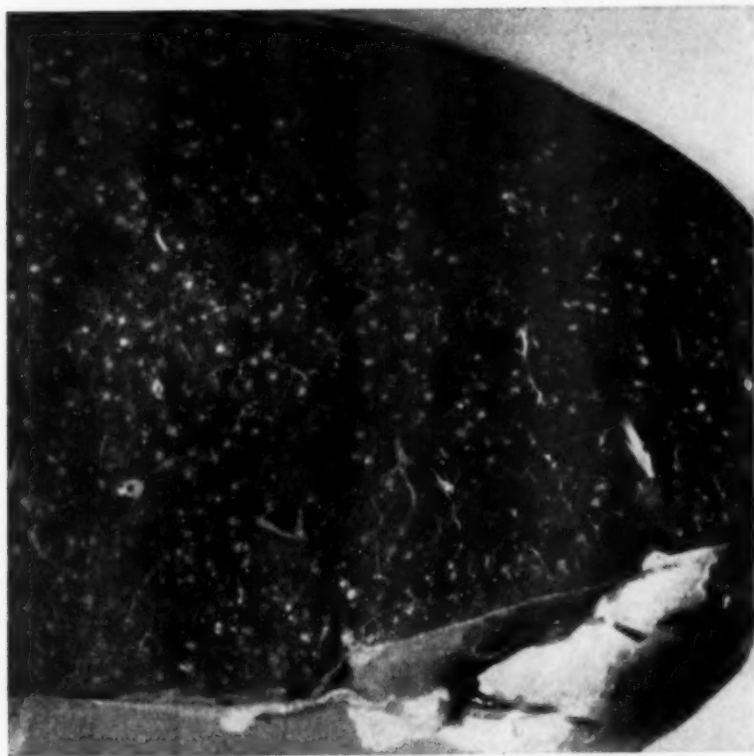


FIG. 10. Case 2. Cut surface of spleen showing numerous Malpighian corpuscles.

before the above weight was taken; this indicated the marked congestion present in the spleen. The cut surface was dark red, with numerous Malpighian corpuscles (figure 10).

Microscopically the Malpighian corpuscles were large and had unusually large germinal centers (figure 11). They were made up of large proliferated reticulum cells with poorly defined cytoplasm but large, definite nuclei (figure 12). Only occasional mitosis was seen. The sinusoids were moderately dilated and appeared rigid, as though the dilatation had been present for some time. The sinusoids were filled with erythrocytes (figure 13). There was slight fibrosis of the pulp between

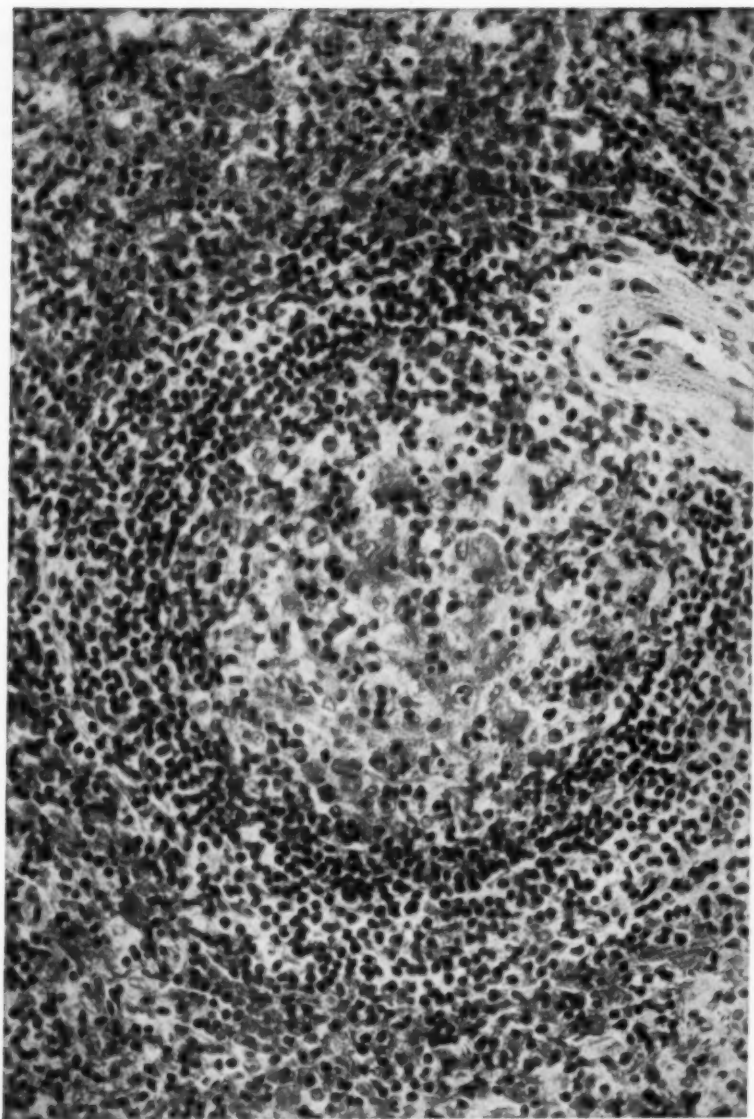


FIG. 11. Case 2. Microscopic section of spleen showing large Malpighian corpuscle with unusually large germinal center.

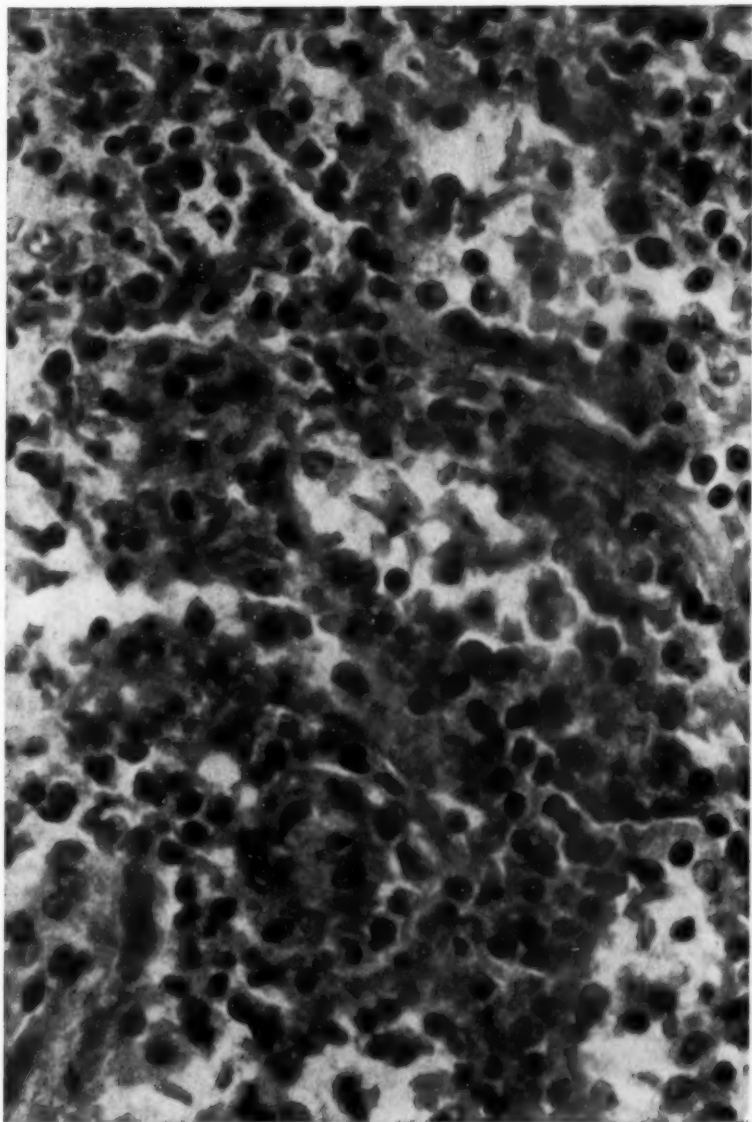


FIG. 12. Case 2. The germinal centers were made up of large reticulum cells with poorly defined cytoplasm.

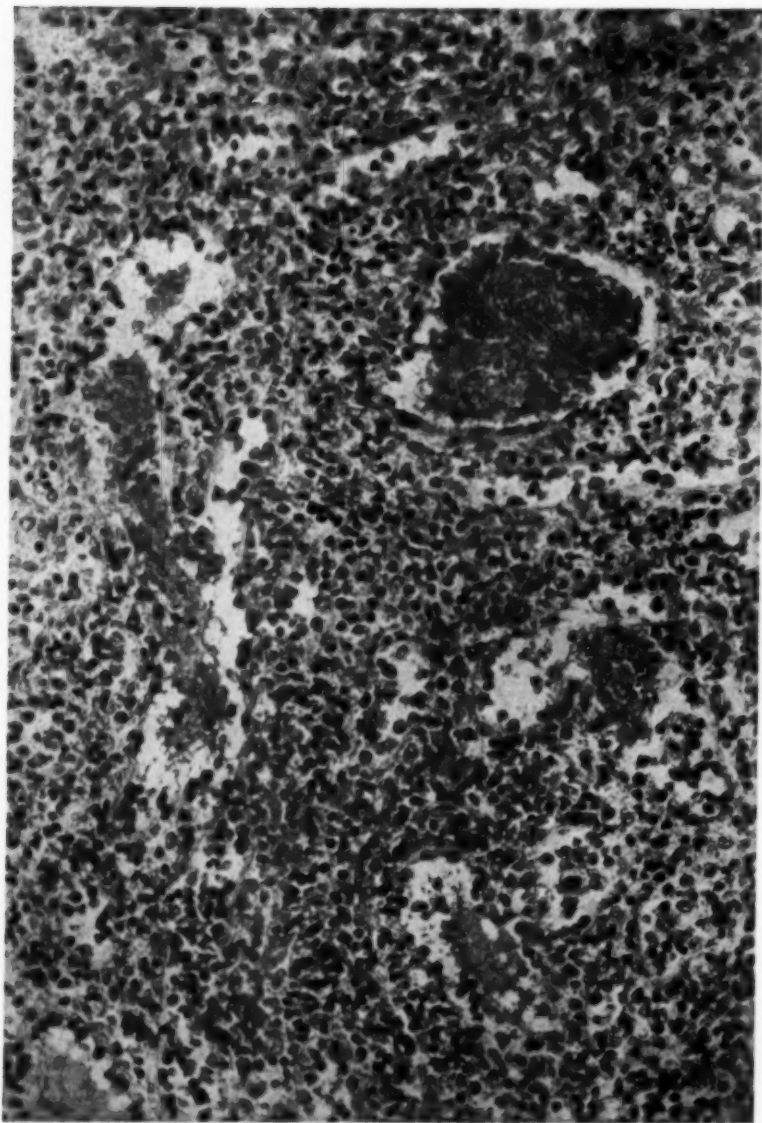


FIG. 13. Case 2. The splenic sinusoids were filled with erythrocytes.

the sinusoids. A rare giant cell (probably a megakaryocyte) and a few eosinophilic leukocytes were noted. No myeloid metaplasia was present. The arteries were essentially normal. The trabeculae were slightly thickened.

Diagnosis: (1) Congestive splenomegaly. (2) Slight reticuloendothelial hyperplasia.

The table that follows shows the various blood studies done before and after splenectomy:

There has been a follow-up of this patient to date through the courtesy of her family physician, Dr. Frank T. Linz, of Tampa, Florida. Her red count, hemoglobin and white blood count have been normally maintained; however, there has been some drop in the platelets. Her general condition, including her joints, has been excellent. Relief of joint symptoms occurred immediately postoperatively and has been maintained to date.

TABLE II
Case 2, Six Months' History of Painful Swollen Joints

Date	RBC	Hb.	WBC	Platelet	Sed. Rate
4/28/51	4,560,000	13.0 gm.	2,400	260,000	4
5/ 3/51	4,130,000	12.3 gm.	2,050	130,000	
5/ 4/51	SPLENECTOMY. Marrow showed fat, 1 mm.; plasma, 54 mm.; erythromyeloid layer, 11 mm.; hematocrit, 36 mm.; bone marrow smear, normal.				
5/ 5/51	5,030,000	15.1 gm.	11,400	166,000	
5/ 7/51	5,050,000	15.1 gm.	8,300	357,000	
5/ 8/51				505,000	
5/ 9/51				620,000	
5/10/51	4,930,000	13.6 gm.	14,900	600,000	
5/12/51	4,680,000	13.3 gm.	10,700	610,000	42
5/26/51	3,800,000	11.5 gm.	7,750	225,000	
6/ 2/51	4,170,000	11.5 gm.	7,450	210,000	
6/16/51	4,400,000	12.0 gm.	6,800	265,000	3
7/20/51	4,420,000	13.6 gm.	9,900	260,000	
8/10/51	4,410,000	10.7 gm.	9,800	250,000	1
10/31/51	5,050,000	12.6 gm.	5,700		9
2/25/52	4,910,000	13.0 gm.	6,400	161,000	16
5/12/52	4,830,000	13.0 gm.	9,900	200,000	12

Case 3. A 45 year old white female underwent a splenectomy for Felty's syndrome in May, 1940. There was marked improvement in her red blood count, hemoglobin and white blood count after this surgical procedure. She was seen only occasionally thereafter, and it is interesting to record that on September 4, 1943, her blood count was as follows: red blood cells, 3,370,000; hemoglobin, 11.2 gm.; white blood cells, 5,000. Differential: stabs, 2; segs., 16; mononuclears, 73; monocytes, 8; eosinophils, 1. Her platelet count was normal at 290,000. The sedimentation rate was elevated at 1.30 (normal by this method, 0.08 to 0.35).

Her arthritis was not particularly troublesome during this period of approximately three and one-half to four years. However, she was admitted to the Rochester General Hospital February 24, 1944, with acute myelogenous leukemia and died three days later (figures 14 and 15).

Reexamination of the record to see whether we had actually been dealing with a leukemia all the time showed that the sections of the spleen removed and smears of bone marrow aspirated before splenectomy yielded no evidence of leukemia.

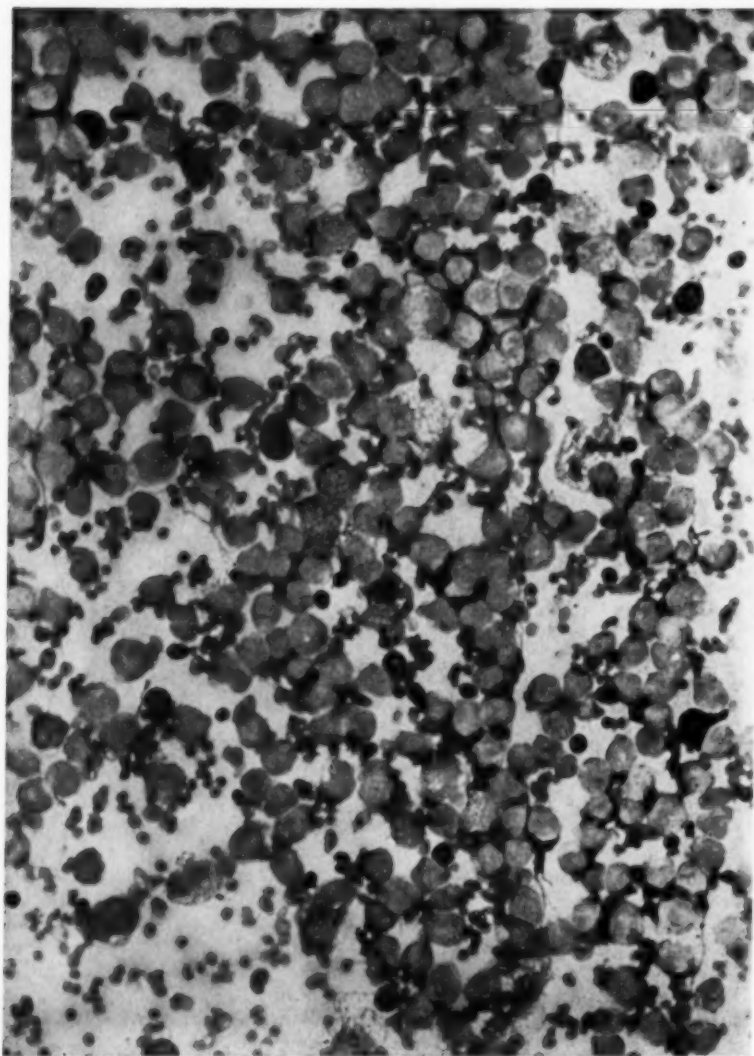


FIG. 14. Case 3. Low power of bone marrow showing myelogenous leukemia.

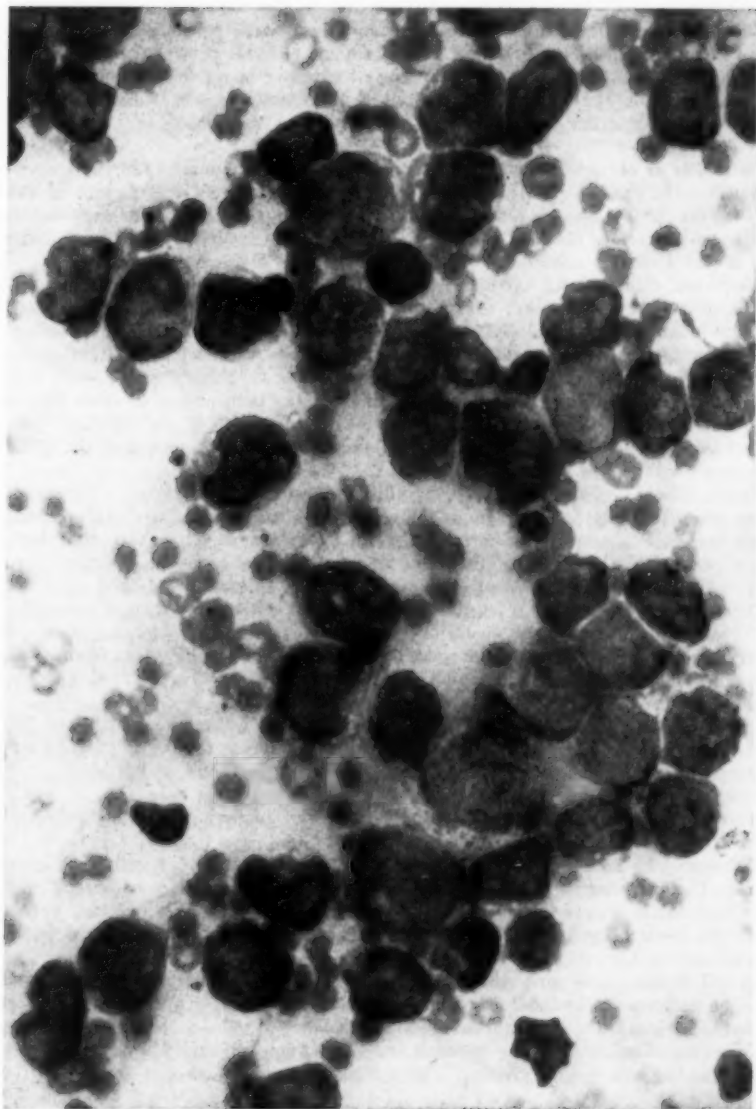


FIG. 15. Case 3. High power of bone marrow showing marked increase in early myelocytic series.

Autopsy:

External Examination: The body was that of a poorly developed, poorly nourished white woman 48 years of age. The skin was pale. Over the anterior left shoulder and chest and on the left arm and both forearms there were petechial hemorrhages. The lips were covered by hemorrhagic crusts. In the anterior part of the chest there were linear cutaneous hemorrhages at the site of adhesive strips. Two and one-half to 3 cm. to the left of the midline of the abdomen there was a well healed white operative scar extending from the rib margin to just below the umbilicus. There was slight edema of the feet.

There was an extreme deformity of the hands and feet, particularly of the former. The wrists were flexed. The phalanges were hyperextended on the dorsum of the hands, and on the left hand reached almost a right angle while the digits were flexed and extended in various fashions. All of the joints in these regions were firmly fixed. The skin was stretched and shiny; the hands were generally somewhat atrophic.

Abdominal Cavity: The left upper quadrant was an intricate mass of adhesions. In the fatty omentum there were several small nodules, 2 to 4 cm. in diameter, made up of soft red tissue which resembled splenic tissue. The spleen itself was missing. The left lobe of the liver was enlarged and extended into the normal position of the spleen. The pelvic organs were extremely pale.

Thoracic Cavity: There were numerous adhesions in both pleural cavities but no fluid. The heart was slightly enlarged. The mediastinum was of normal size. The pericardial sac was practically completely obliterated by firm, fibrous adhesions. The parietal pericardium was thickened.

Heart: The heart weighed 330 gm. The valves were all normal. The myocardium was extremely pale, brown in color, and streaked and speckled with yellow. The left ventricle measured 13.5 mm.; the right, about 4 mm., but it was difficult to measure because the epicardial fat extended into it. The coronary arteries were smooth. The aorta was 60 mm. in circumference at its origin, smooth and pale.

Right Lung: There were a few blebs of air on the anterior surface of the upper lobe. The lower lobe and the posterior part of the upper contained an increased amount of fluid but were otherwise normal. *Left Lung:* The left lung was identical to the right. The tracheobronchial lymph nodes were only slightly enlarged and appeared edematous.

Liver: The liver weighed 1,350 gm. The right lobe was rather small, the left relatively increased in size. There were many adhesions over the left lobe. On section the parenchyma was rather homogeneous, orange-brown, soft and friable.

Gallbladder: Gallbladder was normal.

Adrenals: The adrenals were of usual size. The cortices were very pale and contained little grossly visible lipid.

Kidneys: The kidneys were of approximately equal size and together weighed 350 gm. The capsules stripped readily but took small amounts of renal tissue with them. The surfaces were fairly smooth and extremely pale. On section, cortex and medulla could scarcely be differentiated; both were pale, brownish. Renal pelves were normal.

Lymph Nodes: The periaortic nodes were very slightly enlarged, dark red and soft. The peripancreatic nodes were moderately enlarged and grayer. The cervical nodes were very small. No other enlarged nodes were found.

Gastrointestinal Tract: The stomach was moderately distended and the mucosa thin, but the rugae were still visible. The pylorus was normal, as was the rest of the tract.

Bone Marrow: The marrow from the middle of the right femur was very abundant and gray, in places appearing almost purulent. The cancellous bone was almost completely gone, the cortex thin but hard. The marrow of the sternum was similarly abundant, soft and gray, but could be taken out in chunks like tissue.

Internal Genitalia: Essentially normal, atrophic.

Thyroid: The thyroid weighed 55 gm. and was made up of numerous nodules, some containing large amounts of colloid, others in part calcified.

Throat: Palpation with one finger through the aperture of the larynx and one in the mouth disclosed a normal tongue and complete absence of obstruction.

Spine: Cross examination of spinal column showed no evidence of pathology. There is not even slight lippling of bone margins.

Review of Spleen Removed at Operation in 1940: We received a spleen measuring 14 by 9 by 4.5 cm. Cut section was dark red and apparently normal. The Malpighian corpuscles were small.

Microscopic: Malpighian corpuscles were essentially normal, as were their central arterioles. There were very occasional histiocytes containing some iron pigment, especially around the arterioles.

The pulp showed an intense hemosiderosis. Numerous swollen reticulum cells contained dark brown pigment which gave a Prussian blue reaction. Only a small number of other (lymphoid) splenocytes were seen. The sinusoids were not very prominent; they were collapsed, but lined by somewhat swollen littoral cells which contained moderate amounts of iron. There was no evidence of fibrosis and only very occasional eosinophilic leukocytes. No leukemic cells were seen.

Microscopic:

Bone Marrow: The marrow from the sternum and that from the femur were exceedingly and equally cellular. Most of the cells were myeloblasts, with relatively large nuclei made up of well formed chromatin reticulum, one or more nucleoli, and thin rims of cytoplasm. Of the other cells present, most were myelocytes (neutrophil and eosinophil). Only occasional islands of erythrocytopoietic cells were present. Megakaryocytes were present, but in markedly reduced numbers.

Section of the fatty marrow of a finger showed small numbers of myeloblasts among the fat cells and tiny islands of more active hematopoiesis made up almost entirely of myeloblasts. Wherever these cells occurred, they seemed to be in close relation to blood capillaries.

One section of sternum was apparently taken through the site of the previous sternal puncture. The thin cortex was here covered by irregular thin lamellae of bone, between which there was still some granular debris.

Liver: The cells near the portal areas were large, and separated by rather narrow sinusoids; those in the centers of the lobules were smaller and contained fat globules, and were separated by wide sinusoids. Many of the liver cells, especially in the periphery of the lobule, contained fine brown pigment granules.

The Kupffer cells were very prominent and numerous, and every one contained hemosiderin, as though in an injection experiment with colloidal iron. Most were still moderately flat or branched, but a few were very large and rounded, and practically filled the sinusoids into which they extended; these contained large masses of hemosiderin, usually in larger granules than in the smaller Kupffer cells.

There was no evidence of hematopoiesis or leukemic infiltration in the liver.

Lymph Nodes: The nodes were all small or only very slightly enlarged, and varied somewhat in appearance. However, some of the tracheobronchial nodes and all of the other nodes examined showed very intense hemosiderosis. The sinuses were lined by and contained cells filled with blood pigment, while other such cells, fewer in number, were found in the follicles.

Some of the pigment containing nodes were otherwise uninvolved; specifically, they showed no leukemic transformation. Many nodes, however, showed mild leukemic transformation, often very slight. Usually the small nodes of myeloblasts and eosinophilic myelocytes were in the medullary portion of the node.

Splenic Tissue: The nodules of soft red tissue seen grossly in the left upper quadrant were histologically reminiscent of splenic tissue. Each was surrounded by a fibrous capsule containing islands of hemosiderin-filled macrophages. In their substances sinusoids and pulp were identifiable, but there were only a few arterioles and no lymphoid collections resembling Malpighian corpuscles. There were a few connective tissue trabeculae.

The sinusoids were well defined and lined by littoral cells which were large, almost cuboidal. Some of the lining cells contained moderate amounts of hemosiderin. Seldom did the lumens of the sinusoids contain more than a rare cell. The pulp between sinusoids was for the most part made up of groups of very large macrophages packed with hemosiderin granules. A few small reticulum cells and lymphoid cells made up the rest of this tissue. There were no leukemic cells and no myeloid metaplasia.

Thyroid: The lobules were separated by increased amounts of fibrous tissue. The alveoli were filled with homogeneous colloid and lined by flat cells.

Pancreas: Acini were normal. There was an increased amount of fat between lobules.

Heart: Essentially uninvolved.

Kidney: There were a few obliterated glomeruli, some in groups beneath the capsule, marked by indentation and contraction of the capsule and surrounded by collapsed tubules, a few in the interior of the kidney. The kidney tubules showed large amounts of iron pigment, almost entirely within the convoluted tubules. In part, this was in the form of fine to coarse brown granules which gave a typical Prussian blue reaction, but even more was apparently in solution within the cells, for the cytoplasm stained almost diffusely blue by Perl's method. Considerable non-granular and a little granular iron was present in the lumens of the convoluted tubules.

TABLE III

Case 4, a 10 Year History of Rheumatoid Arthritis (1950)

Date	RBC	Hb.	WBC	Sed. Rate
1944	4,350,000	11.0 gm.	6,600	22
	to	to	to	
	4,480,000	12.9 gm.	6,900	
1945	4,320,000	12.8 gm.	5,900	15
	to	to	to	
	4,470,000	13.0 gm.	7,700	20
1946	4,480,000	12.7 gm.	5,400	5
	to	to	to	
	4,610,000	13.1 gm.	6,600	25
1947 to 1948	NO OBSERVATION			
3/16/49	4,580,000	11.6 gm.	3,200	
3/30/49	4,810,000	11.5 gm.	2,000	19
4/ 6/49	(Spleen felt three fingerbreadths below left costal margin.)			
4/ 6/49	Normal bone marrow.			
1950	4,070,000	11.6 gm.	3,550	25
	to	to	to	
	4,780,000	13.4 gm.	4,350	34
1951	4,210,000	13.1 gm.	5,050	4
	to	to	to	
	5,020,000	14.8 gm.	7,100	23

TABLE IV

Case 5

(The values of the various cellular elements represent the highest and lowest figure for each year of observation)

Date	RBC	Hb.	WBC	Platelet	Sed. Rate
1944	4,500,000	13.3 gm.	8,400	none	27
	to	to	to		
	4,920,000	14.4 gm.	13,500		
1945	4,540,000	13.4 gm.	7,700	315,000	7
	to	to	to		
	4,710,000	14.4 gm.	10,000		
1946	4,410,000	12.6 gm.	6,400	360,000	8
		to	to		
	(One determination)		8,000		
1947	NO OBSERVATION				
1948	4,880,000	13.7 gm.	11,300	360,000	13
	to	to	to	to	to
	4,930,000	14.0 gm.	11,400	400,000	25
1949	4,890,000	14.2 gm.	9,600	380,000	13
	to	to	to	to	to
	4,940,000	14.7 gm.	11,250	520,000	17
1950	4,350,000	12.6 gm.	10,450	285,000	4
	to	to	to	to	to
	4,550,000	13.4 gm.	12,000	480,000	28
1951	4,450,000	12.5 gm.	7,500	289,000	23
	to	to	to	to	to
	4,840,000	14.0 gm.	16,550	480,000	30
1952 (2-5-52)	5,160,000	13.3 gm.	6,350	370,000	30

April 14, 1952, the spleen was first felt three fingerbreadths below the left costal margin.

4/14/52	5,320,000	14.0 gm.	3,200	220,000	38
4/18/52			2,900	180,000	
4/29/52	5,700,000	13.6 gm.	6,600	185,000	

Sternal marrow aspirations September 10, 1948, and April 15, 1952, were normal.

There were very small cellular infiltrations containing a few myeloblasts. These were found beneath the capsule around the obliterated glomeruli and, to a lesser extent, in the interior within the interstitial tissue. None of the infiltrates was large.

Bone: Sections were obtained from one of the badly deformed fingers. The cortex was very thin. The loose, cancellous marrow tissue contained foci of leukemic transformation as described above. The cartilage of the interphalangeal joint was thin and in places gone. The cartilaginous surface of one bone had slipped forward off the articular cartilage of the adjacent one. From the periphery, dense connective tissue bound the adjacent bones together in their abnormal position.

The following cases show the effects of cortisone and corticotropin in rheumatoid arthritis associated with splenomegaly:

Case 4. A 41 year old white female with a 10 year history of rheumatoid arthritis was treated Class IV according to the Steinbrocker classification (bedridden case). This patient with advanced rheumatoid arthritis, iron deficiency anemia and leukopenia was treated with 100 mg. of cortisone daily from February 1 until August 30,

1951, a period of six months. The spleen, which had been felt three fingerbreadths below the costal margin, the white blood count, which had ranged from 2,000 to 4,350, and the iron deficiency anemia all returned to normal. However, four weeks after cessation of cortisone the spleen was felt three fingerbreadths below the costal margin and the white blood count dropped from 7,100 to 4,650.

Case 5. A 40 year old white female had a 14 year history of rheumatoid arthritis and was rated Class III according to the Steinbrocker classification. Treatment with gold thioglucose, gold thiosulfate, gold thioglycolanalide, streptococcal vaccine, terramycin and large doses of vitamin C (5.4 gm. per day), with added large doses of calcium panthothenate (5.4 gm. per day), resulted in no definite clinical improvement.

Splenomegaly was first found on April 14, 1952. At that time the patient's white blood count had dropped to 3,200, and a few days later the platelet count had dropped to 180,000. The spleen was felt three fingerbreadths below the costal margin.

TABLE V

Case 6, 15 Year History of Rheumatoid Arthritis. Given 20 units of ACTH intravenously daily from 6/28/51 to 7/26/51

Date	WBC	Hb.	RBC	Eos.	Sed. Rate
6/27/51	3,210,000	4.6 gm.	3,850		14
6/29/51			4,500	22	
7/ 3/51	3,390,000	6.1 gm.	4,800	77	
7/ 9/51	3,130,000	5.0 gm.	5,900	77	30
7/10/51	Oral ferrous sulfate started.				
7/14/51	3,130,000	6.5 gm.	5,400	77	51
7/16/51	1.5 c.c. saccharated ferrous oxide given intravenously.				
7/17/51	3 c.c. saccharated ferrous oxide given intravenously.				
7/18/51	3,940,000	6.1 gm.	5,300		
7/19/51	5 c.c. saccharated ferrous oxide given intravenously.				
7/19/51	3,880,000	6.1 gm.			
7/23/51	4,020,000	6.5 gm.			
7/24/51	500 c.c. of blood given by transfusion.				43
8/22/51	4,470,000	11.9 gm.	9,900		
8/28/51	Spleen palpable one fingerbreadth below the left costal margin.				

An attempt to determine the size of the spleen by a radiograph was unsatisfactory because the patient was unusually thin. (Unless a great amount of fat is present in the abdomen, the spleen is not well visualized.) It was interesting that she had been on cortisone in a dose of 100 mg. daily by mouth from January 8, 1951, until May 15, 1951. The only beneficial effects noted during this period were an increase in appetite and well being; there was very little change in her joints. The only effective steroid therapy was the injection of 37.5 mg. of hydrocortisone into the right elbow and right shoulder, which resulted in marked diminution of pain but no increase in range of motion. The splenomegaly, leukopenia and thrombocytopenia developed approximately 11 months after cessation of cortisone therapy. At least it might be said that cortisone did not prevent the production of this syndrome. It is to be admitted that this was a rather long period after cortisone therapy had been instituted; on the other hand, the cortisone was given in adequate amount and over a period of four months.

Case 6. A 42 year old white female with a 15 year history of rheumatoid arthritis was rated Class III according to the Steinbrocker classification. Table 5 shows

the hematologic picture as observed before and after the splenomegaly associated with leukopenia. She was given an injection of 20 units of corticotropin in 500 c.c. of 5 per cent glucose daily for 30 days.

Cortisone and corticotropin result in temporary improvement in the blood picture and diminution of the spleen in cases of rheumatoid arthritis associated with splenomegaly and leukopenia. There is evidence to indicate that this medication does not prevent the onset of the syndrome and does not result in the permanent reversal of the syndrome. Splenectomy appears to be the treatment of choice in these cases. Evidence is presented to suggest that the removal of the spleen results in hypertrophy of the anterior lobe of the pituitary. If this be true, then the procedure actually sets in motion a constant and increased supply of corticotropin in the individuals. A new method of approach to the problem of rheumatoid arthritis therapy is suggested in this paper.

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FURTHER STUDIES ON ELECTROCEREBRAL DYS-FUNCTION AND THE USE OF ANTICONVULSANTS IN LABILE DIABETES*

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THE brittle or labile diabetics pose a difficult problem even to physicians experienced in the treatment of diabetes. Such patients exhibit an extreme instability of their blood glucose regulation and, as previously shown,¹ may be subject to pseudohypoglycemic reactions, that is, reactions which occur with normal or elevated blood glucose values and are refractory to carbohydrate administration. Inasmuch as most of our labile diabetics had electroencephalographic abnormalities that could not be ascribed to the immediate hypoglycemic effect of insulin or to diabetes per se, we have been led to the use of anticonvulsive drugs, which have proved highly effective in the management of such patients.

MATERIAL AND PROCEDURE

The present investigation concerns a group of 15 labile diabetics with no family history of epilepsy and, with two exceptions (cases 4 and 5), with no history of convulsions prior to onset of diabetes. At first we used a 3-channel Grass Electroencephalograph; then from July, 1947, to October, 1950, a 6-channel, and since then an 8-channel instrument. The criteria for determining abnormal electroactivity were the same as described previously.^{1,2} To avoid subnormal blood glucose values, the tracings were taken one to two hours after a normal meal. Drugs apt to modify the brain wave pattern, such as barbiturates, benzedrine, etc., if used, were discontinued for at least a week prior to the tests. Since hypocalcemia may produce abnormal brain potentials,^{3,4,5,6} serum calcium determinations were made in all subjects in the two weeks before the electroencephalograms were recorded. Dilantin, Mesantoin, Mebaral and phenobarbital were the anticonvulsive drugs used.

CASE REPORTS

Since the case histories previously presented¹ illustrate well the nature of labile diabetes, only three cases in which particular difficulties were encountered are here briefly reported.

Case 4. A 14 year old white girl, with a history of childhood convulsions which ceased following tonsillectomy at the age of five, developed diabetes when she was

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nine. Placed on a 2,000 calorie diet with 30 units of protamine zinc insulin, within a week she experienced her first insulin reaction with convulsions and loss of consciousness which lasted over 15 hours in spite of oral and intravenous glucose administration. From then on she was subject to muscle twitches during her sleep, even though for six months she took only 12 units of protamine zinc insulin daily because of fear of major seizures, and almost all her urine specimens contained sugar. On 20 to 24 units of insulin, massive glycosuria was interspersed with occasional severe and frequent milder reactions which were relieved by taking orange juice with sugar.

When first seen a year after the onset of her diabetes, she felt extremely weak and weighed 76½ pounds for a height of 58½ inches. Given 34 units of protamine zinc insulin with 12 units of regular insulin, she remained free from attacks for one month but in the following 10 days had two seizures, with rigidity and unconsciousness which responded to carbohydrate administration. An electroencephalogram was found mildly abnormal and the serum calcium low (7 mg. per cent). When the latter was raised to 11.5 mg. per cent the night twitches subsided but the insulin reactions continued. During one reaction she bit her tongue and responded poorly to glucose, and the blood glucose content 13 hours after the reaction did not exceed 80 mg. per cent. Dilantin was then prescribed, and a year later both the serum calcium and the electroencephalogram were within normal limits. Even though the insulin dosage was increased during that year to 60 units daily, she had fewer reactions and became more resistant to hypoglycemia, so that on occasions she remained symptom-free with blood glucose values of 50 and 55 mg. per cent. Owing to the better control of her diabetes she gained in weight to 104½ pounds and in height to 63¼ inches. Then because of family difficulties she abandoned all therapy, took insulin irregularly and again became subject to severe reactions. A control tracing showed progressive deterioration of the electroencephalogram, even though her serum calcium remained normal.

Case 5. This 38 year old white woman developed diabetes at the age of 32, with all the classic symptoms and a loss of 32 pounds in weight in two months. Given a diet and 40 units of protamine zinc insulin, she regained 15 pounds in five weeks but was having attacks of convulsions with unconsciousness. In a year she was hospitalized five times and each time the attacks were diagnosed as diabetic coma, as they were associated with blood sugar readings of 239 to 377 mg. per cent and a heavy glycosuria. Her seizures were preceded for one to two days by glycosuria and were apt to occur particularly a week before her menstrual periods. They interfered greatly with her work as an operator in a dress factory.

When she was first seen, three years after the onset of her diabetes, a history of convulsions in childhood and of automatic behavior and blank spells in recent years was elicited. She was depressed and crying continuously, and on physical examination insulin lipodystrophies on her arms and thighs were striking. X-ray examination of the skull was negative and the electroencephalogram was mildly abnormal. The patient was given Dilantin and phenobarbital, but after a year and 10 months she was continued on phenobarbital alone. Her insulin dosage at first was 44 units of protamine zinc with 16 units of regular insulin, and for the past year and a half between 50 and 60 units of NPH insulin.

In the more than three years since the institution of anticonvulsive therapy she has had only two major seizures with convulsions and tongue biting, namely, one following extraction of an abscessed tooth, in June, 1949, and another in January, 1951, during which the blood glucose content was 35 mg. per cent. However, she still is troubled by occasional mild reactions (shakiness, dizziness, crying spells), occurring at mealtime and relieved by taking food. A control electroencephalogram done at the time she was taking Dilantin was considered as consistent with convulsive tendency. Nevertheless, she presents no behavior disorders and has been able to resume her work.

Case 6. This 28 year old white woman exhibited personality disorders long before the onset of her diabetes. Soon after she was born her mother left the family and the patient was reared by her aunt and uncle, people of rigid mentality and strict behavior. She "had always been very depressed and moody, and never knew a happy medium." In 1944, at the age of 20, she married a soldier, but her husband was soon shipped abroad and when he returned two years later she realized that "it was one of those war marriages." She sustained a terrible shock on seeing her dream of a family life of her own shattered, and after a year's separation started divorce proceedings which to her, as a Catholic, were abhorrent. It was around that time (age 23) that she developed diabetes. On a 2,000 calorie diet with biweekly B-complex injections, her condition deteriorated rapidly and she suffered from cramps in her legs, paresthesias in her hands, blurred vision and "a hysterical behavior." With the addition of 15 to 20 units of protamine zinc insulin daily, mild insulin reactions appeared but her diabetes remained uncontrolled.

When first seen, a year after the onset of her diabetes, she complained of rectal and vaginal itch, swelling of inguinal lymph glands and weakness so extreme that she "could hardly carry a book." Extensive insulin lipodystrophies were noted in her thighs, and the blood sugar was up to 347 mg. per cent. She was taught the proper technic of injecting the insulin to avoid local reactions to this hormone; and, without a change in her diet, 38 units of protamine zinc and 10 units of regular insulin were prescribed. At first she was cooperative, but three months later neglected the diet, increased the insulin dosage and gained 20 pounds in two months. Soon there appeared frequent episodes of what she thought to be insulin reactions, namely, depression, crying and screaming spells, throwing things at people and automatic behavior with retrograde amnesia. The attacks usually occurred around 10:00 a.m. and, if lunch was omitted, around 2:00 p.m. They were often accompanied by sweating and trembling, were more frequent seven to 10 days before her menstrual periods, and, though partly relieved by taking food, lacked any correlation with the height of the blood sugar. During one attack, for instance, the blood glucose was 150 mg. per cent and during another one, a half-hour after breakfast, 163 mg. per cent, and 112 mg. per cent two hours later; while during two other attacks it was 78 and 35 mg. per cent.

Because of absence of critical hypoglycemia in some of her attacks, and because of the history of "hysterical" episodes even before the institution of insulin therapy, an electroencephalogram was taken. This revealed a borderline pattern with no evidence or suggestion of convulsive tendency. On Dilantin, which she took for only two weeks, she had daily crying spells, but on Mebaral her attacks became less violent. Her insulin dose varied from 40 to 50 units daily. In April, 1950, her family sent her to Boston, where a complete check-up, including lumbar puncture, an arteriogram and a pneumoencephalogram, was negative, and the electroencephalogram was interpreted as consistent with an atypical seizure disorder. A small meningioma was suspected and she was again placed on Dilantin. Upon her return to New York she complained of lapses of memory and difficulty in remembering people's names and faces. When Mebaral was substituted for Dilantin she was somewhat improved and less tense and less depressed, but she remained utterly uncooperative and took the treatment of her diabetes into her own hands.

In May, 1951, she was admitted to the University Hospital for reevaluation. On 50 units of NPH with 10 units of regular insulin there was no change in the lability of her diabetes. Bouts of heavy glycosuria, with the blood glucose rising to 290 mg. per cent, alternated with unpredictable insulin reactions during which it descended to 35 mg. per cent. The histamine test for pheochromocytoma was negative, the 24 hour excretion of 17-ketosteroids 12 mg., and a control electroencephalogram showed a pattern which could be consistent with convulsive tendency. We felt, however, that this was not a case of clear-cut convulsive disorder, and were convinced that this

TABLE I
Electroencephalographic Patterns in 15 Cases of Labile Diabetes

Case	Sex	Age at Onset of Diabetes	Initial Electroencephalogram		Repeat Electroencephalograms	
			Duration of Diabetes	Date and Type of Tracing	Date and Type of Tracing	Date and Type of Tracing
1. D. A. H.	M.	35 yrs.	14 yrs.	6-17-46 Epileptogenic focus	11-11-47 Borderline	
2. R. H.	F.	24 yrs.	6 yrs.	6-26-46 Mildly abnormal	8-7-51 Normal	
3. C. J. S.	F.	31 yrs.	6 yrs.	9-30-46 Mildly abnormal	10-17-47 Normal	2-7-49 Normal
4. M. C.	F.	9 yrs.	1 yr.	4-20-48 Mildly abnormal	1-24-50 Normal	2-19-51 Focal pathology
5. B. L.	F.	24 yrs.	3 yrs.	2-3-49 Mildly abnormal	3-1-49 Mildly abnormal	1-11-51 More abnormal
6. B. A.	F.	10 yrs.	24 yrs.	10-11-46 Mildly abnormal	11-24-50 More abnormal	
7. E. T.	F.	23 yrs.	2 yrs.	1-11-49 Mildly abnormal	4-6-50 Atypical seizure pattern	5-8-51 Convulsive tendency
8. S. S. K.	M.	34 yrs.	14 yrs.	12-11-46 Mildly abnormal		
9. M. A. R.	M.	20 yrs.	17 yrs.	5-9-52 Mildly abnormal		
10. J. G.	M.	11 yrs.	22 yrs.	5-19-52 Convulsive tendency		
11. T. C.	M.	24 yrs.	8 yrs.	7-19-51 Convulsive tendency and focal pathology	9-15-52 Borderline	
12. M. L.	F.	41 yrs.	7 yrs.	8-7-46 Convulsive tendency	4-18-52 Focal pathology	9-8-52 Mildly abnormal
13. R. L. S.	M.	23 yrs.	11 yrs.	7-2-46 Normal		
14. J. H. M.	M.	28 yrs.	11 yrs.	10-19-51 Normal	4-4-51 Normal	
15. J. A. E.	M.	23 yrs.	14 yrs.	6-26-51 Normal		

patient's main difficulty was a long-standing primary compulsive neurosis with hysterical outbursts, and that at times subnormal blood sugar levels may have acted as a trigger mechanism in bringing on such outbursts. We therefore suggested psychotherapy, but this was refused by the patient.

Results of Laboratory Studies: Hypocalcemia of 7 mg. per cent was recorded in only one patient (case 4). Results of electroencephalographic investigations are presented in the table.

DISCUSSION

1. *Occurrence and Nature of Electrocerebral Dysfunction in Labile Diabetes:* Absence of electroencephalographic abnormalities in three patients of this series (cases 13, 14, 15) indicates that abnormal brain potentials are not the prerequisite of lability in diabetes. However, it is of interest that a long history of 11 to 14 years of repeated severe insulin reactions left no imprint on the electrocerebral activity of these patients. One can only speculate whether they have sustained transient and reversible brain changes which were not reflected in the recorded electroencephalograms.

Abnormal initial tracings were found in 80 per cent of patients herein reported, and were classified as mildly abnormal in eight, consistent with convulsive tendency in three, and indicative of an epileptogenic focus in two (cases 1 and 11).

Progressive distortion of cerebral electroactivity was observed in four patients who received no anticonvulsive therapy or who took anticonvulsants

irregularly (cases 4, 6, 7, 12), and in one who showed a satisfactory clinical response to continuous administration of anticonvulsants (case 5). Thus, patterns with more than mild abnormalities and mostly consistent with convulsive tendency or focal pathology were obtained in seven untreated or inadequately treated patients (cases 1, 4, 6, 7, 10, 11, 12), that is, in almost 50 per cent of all patients. The interpretation of repeat tracings in case 5 is difficult in view of her history of childhood convulsions.

While no sufficient information is available as yet to explain satisfactorily the absence as well as the development of abnormal brain potentials in labile diabetes, certain known facts appear to be significant in this regard. Extension of our study to blood relatives of patients herein reported allowed the detection of electrocerebral dysfunction in three families, namely, in two daughters of case 12, one sister of case 6 and three sisters of case 2. Since the blood relatives of these patients suffered from spontaneous hypoglycemia, we have concluded that the abnormal brain waves in these three diabetics were not related to diabetes per se, and we have suggested that they may have been genetic or constitutional in origin.¹

It has been well established that hypoglycemia interferes with normal brain function by curtailing the supply of glucose to the brain and so reducing the cerebral oxidative metabolism. In acute hypoglycemia there is a decrease in the amount of normal brain waves, which are replaced by slow activity of 3 to 5 cycles per second.^{7, 8, 9, 10, 11, 12} These changes in the electroencephalogram are considered as reliable manifestations of hypoglycemia, but a better correlation may be obtained between the alterations of brain potentials and the reduced oxygen utilization by the brain.^{9, 13, 14} Administration of glucose in acute hypoglycemia may restore the electroencephalogram to normal without a significant change in the blood glucose content,^{9, 15} while in prolonged hypoglycemic coma the abnormal brain waves may persist even when it is raised to normal or definitely hyperglycemic levels.^{13, 15, 16, 17} Lastly, it is also known that critically low blood glucose values may be accompanied by perfectly normal electroencephalograms.^{15, 18}

While there is thus no strict parallelism between the height of the blood glucose and the electrocerebral activity, it must be appreciated that severe and prolonged hypoglycemic episodes may produce injury to the brain. The resulting changes in the metabolism and function of the neuronal cell may account for the persistence of electroencephalographic abnormalities after the decline in blood glucose has been corrected. In fatal post-hypoglycemic coma, Fazekas et al.¹⁹ recorded abnormal brain potentials along with a progressive depression of cerebral oxygen consumption. Since they found adequate amounts of glucose and oxygen in the arterial blood which reaches the brain, they concluded that the diminished oxygen uptake by the brain was due to an impairment of cerebral enzymatic activity. Their conclusion supports our concept that a hypoglycemic reaction cannot be explained solely in terms of quantitative changes in the blood glucose, and that basically it represents the clinical counterpart of metabolic and functional derangements

of the brain cell.¹⁹ This concept also finds good support in the demonstration that severe hypoglycemic reactions which become refractory to carbohydrate administration may be favorably influenced by blood transfusions or intravenous administration of liver extract, procedures which restore the ability of the brain to consume and utilize glucose and oxygen.²⁰

From these facts it is clear that brain waves recorded during or shortly after a hypoglycemic reaction may reveal temporary abnormalities unrelated to the basic defect of labile diabetes. Since we have avoided the immediate effects of hypoglycemia on the cerebral electroactivity, and since we have found electroencephalographic alterations in some of our patients in apparent absence of a genetic factor, we believe that a proportion of electroencephalographic abnormalities recorded in our patients were secondary to repeated severe insulin reactions, and that they reflect brain changes sustained as a result of the severe hypoglycemic episodes.

2. *Effect of Electrocerebral Dysfunction on the Course of Diabetes:* The present study confirmed previous observations on the occurrence of pseudohypoglycemic reactions in labile diabetes.¹ Such reactions develop in the absence of hypoglycemia and can be ascribed to electrocerebral dysfunction itself. Mistaken for virtual hypoglycemic reactions, they induce patients to take excessive amounts of food and in this way interfere with proper control of the diabetes.

In the present series we were again able to observe that the disordered electrocerebral activity may intensify virtual hypoglycemic episodes and render them resistant to carbohydrate therapy. Thus, during severe reactions in cases 2, 4, 5, 7, 10, 11 and 12, the blood sugar content ranged from 20 to 43 mg. per cent but the response to the administered carbohydrates was so slow that from two to 15 hours were needed to terminate the reactions. Moreover, these reactions tended to mimic grand mal seizures, with convulsions accompanied by screaming, tongue biting and frothing at the mouth. Clearly, were it not for the laboratory evidence of hypoglycemia they would make one doubtful about their real hypoglycemic nature.

Lastly, because of the abnormal brain waves the patients became susceptible to reactions developing with blood glucose values of 70 to 115 mg. per cent. This lowering of the reaction threshold is analogous to that which we have reported in spontaneous hypoglycemia² and to that described by Thorn²¹ in Addison's disease. That the cerebral dysfunction was involved in lowering of the reaction threshold is evident from improvement in the electroencephalogram, along with an acquired resistance to minor declines in the blood glucose content which followed the use of anticonvulsants in spontaneous hypoglycemia and labile diabetes,^{1, 2} or the use of adrenocortical extract or cortisone in Addison's disease.^{21, 22}

It is also significant that no lowering of the reaction threshold and no pseudohypoglycemic reactions were noted in those patients of our series who failed to exhibit abnormal cortical potentials. The blood sugar content during their reactions was found to be consistently low.

3. *Correlation Between the Electroencephalographic Abnormalities and the Clinical Aspects of Diabetes:* No strict parallelism could be established between the severity of diabetes and the type and degree of electrocerebral disorders, inasmuch as initially normal as well as mildly abnormal or greatly disordered tracings were obtained in this series of severely labile diabetics. On the other hand, a marked distortion of the brain waves pattern was seen only in those with a history of repeated severe insulin reactions.

In a recent study of 77 diabetics and four subjects with mildly abnormal glucose tolerance tests but free from clinical manifestations of diabetes, Izzo et al.²³ concluded that the abnormal electroencephalogram bears no relation to severity, stability or complications of diabetes. It is significant, however, that their data show a high incidence of abnormal tracings in patients treated with insulin, namely, an incidence of 65 per cent in a group of 35 labile diabetics, and of 70 per cent in a group of 27 nonlabile diabetics. By contrast, only 36 per cent of the remaining 19 subjects treated by diet alone had abnormal tracings. In 30 of their patients who exhibited frequent insulin reactions, the incidence of distorted brain potentials was 70 per cent, a figure not much below that of 80 per cent in our series.

Five of our patients with abnormal electroencephalograms received adequate anticonvulsive therapy, following which an improvement in the brain waves pattern was noted in four (cases 1, 2, 3, 4). Of particular interest in this regard is case 4. At first she adhered to the prescribed therapy and her electroencephalogram reverted to normal. She then abandoned the anticonvulsants, became careless about her diet and insulin, and sustained numerous severe insulin reactions, and a repeat tracing revealed stigmata of focal pathology. Variations in the serum calcium content exerted no influence on the progression of her electrocortical abnormalities as these were noted at the time her serum calcium was restored to normal values. Of interest, too, are cases 11 and 12, in whom patterns of convulsive tendency and focal pathology were recorded while they were having frequent insulin reactions with convulsions and loss of consciousness and, in case 11, occasional tongue biting. Following substitution of NPH for protamine zinc insulin, they remained free from reactions, and control tracings showed no evidence of focal pathology even though no anticonvulsants were used in these cases.

These observations appear to indicate that severely disordered brain waves recorded in labile diabetes do not necessarily represent irreversible injury to the brain. On the other hand, failure of the abnormal brain activity to improve or its progression to more abnormal patterns in spite of satisfactory diabetic control and adequate anticonvulsive therapy may be compatible with some associated condition affecting the brain function, such as epilepsy (which we suspect in our case 5), or with irreversible post-hypoglycemic injury to the brain, as reported by Wilson.²⁴ In one of his labile diabetics, anticonvulsants brought about a remarkable clinical improvement, but three repeat electroencephalograms showed no change from

the initial pattern of profound dysrhythmia; a pneumoencephalogram gave evidence of cortical atrophy.

4. *Effects of Anticonvulsive Therapy:* Of seven patients with abnormal brain waves who were placed on anticonvulsants, two failed to take the drugs regularly, namely, case 7, who had a history of personality disorders "as far back as she could remember," and case 6, whose personality disorders were coupled with marital difficulties. In recent months the latter was able to adhere to the prescribed therapy and a marked improvement occurred in her diabetes. Very satisfactory results were obtained in the remaining five patients (cases 1, 2, 3, 4, 5). An appreciable diminution in the frequency and severity of insulin reactions along with a decrease in insulin requirement led to a better control of their diabetes and to their psychologic rehabilitation. In two patients (cases 2, 3) these favorable effects were maintained for three and four years of observation after the anticonvulsants were discontinued. Case 2 took Dilantin for two years and nine months; case 3, Dilantin and Mesantoin for one year and 11 months. The latter, as a result of regained confidence in herself, resumed active social life, got married and recently gave birth to a premature but perfectly healthy baby. Case 4, as mentioned earlier, responded exceedingly well to treatment with anticonvulsants, but suffered an aggravation of her diabetes accompanied by reappearance of severe electroencephalographic alterations when she abandoned all therapy. The response to anticonvulsive therapy in case 5 was excellent. Case 1 was greatly benefited by the anticonvulsants but died two years ago from cardiorenal complications.

Our observation that some labile diabetics who improved on anticonvulsants may not require the permanent use of such drugs makes it conceivable that such patients sustained only reversible brain changes. Following the elimination of abnormal brain potentials, their electroencephalographic patterns remained normal as long as they were free from severe insulin reactions (cases 2, 3), while recurrence of such reactions was accompanied by reappearance of electroencephalographic abnormalities (case 4). These facts further emphasize that some of the disordered brain waves recorded in labile diabetics are secondary to brain injury from severe hypoglycemic episodes.

No change in lability of diabetes was noted in two patients with normal tracings (cases 13, 14) in whom anticonvulsive drugs were tried for a period of six and eight weeks.

The usefulness of anticonvulsive therapy in labile diabetes with electrocerebral dysfunction was recently confirmed by Wilson.²⁴ In a group of eight labile diabetics he recorded abnormal brain potentials in five and, of these, four derived enormous benefit from this therapy. No response was elicited in the fifth patient or in the three patients with normal tracings. Of considerable interest is his previously mentioned case, in which marked lability was overcome by the use of anticonvulsants so that "her diabetes

was relatively easy to control," even though this patient had irreversible brain atrophy and showed no improvement in her electroencephalogram.

SUMMARY AND CONCLUSIONS

1. In a group of 15 labile diabetics, electroencephalographic abnormalities were recorded in 80 per cent and severely disordered patterns consistent with convulsive tendency or focal pathology in almost 50 per cent of the patients.

2. A genetic factor responsible for the abnormal brain potentials was present in three patients, while in one patient atypical epilepsy was considered as a causative factor. The distorted patterns in the remaining patients were attributed to disturbed brain function resulting from repeated severe insulin reactions.

3. It was shown that the abnormal electrocerebral activity reduced the threshold for insulin reactions, increased their intensity and lowered their responsiveness to carbohydrate therapy. It also produced pseudohypoglycemic reactions occurring in absence of critical hypoglycemia.

4. The effectiveness of anticonvulsive drugs in the management of labile diabetes associated with electrocerebral dysfunction was confirmed. Since in two patients the improvement in the electroencephalogram was maintained for up to four years of observation after discontinuation of anticonvulsive therapy, it was concluded that abnormal brain waves in labile diabetes do not always represent irreversible injury to the brain.

5. Inasmuch as normal electroencephalograms were obtained in three patients of this series and no response to anticonvulsants was noted in two of them, it was concluded that abnormal brain potentials are not the only cause or the prerequisite of lability in diabetes.

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CASE REPORTS

PAPILLARY MUSCLE RUPTURE DUE TO A MYOCARDIAL ABSCESS *

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RUPTURE of a papillary muscle of the heart due to a myocardial abscess is a rare occurrence. To the best of our knowledge, no previous reports of this condition have been published. Papillary muscle rupture from any cause, in fact, is rare, with only 41 cases having been reported previously. Davisson¹ summarized 26 cases which had been reported prior to 1948 and added three of his own. In 1950, two cases were reported by Smith² and one by Schwartz.³ In the same year Askey⁴ reported eight additional cases, bringing the total to 40. A case of rupture of a papillary muscle of the right ventricle due to blunt injury to the chest was reported by Kleberger⁵ in 1920. As this case was not included in the previous reviews, it brings the total number of cases to 41. From 22,000 autopsies carried out in three Maryland hospitals, only two cases of papillary muscle rupture were discovered by Stevenson.⁶ The present report is one of three cases of ruptured papillary muscle found in 11,550 autopsies at the Cleveland City Hospital between January 1, 1932, and January 1, 1952. One case has been published previously,² and the third will be included in the discussion at the end of this report.

CASE REPORT

An 81 year old white man was admitted to the Cleveland City Hospital on July 6, 1950, with acute urinary retention. Two other episodes of urinary retention during the preceding week had been relieved by catheterization. For the preceding two years he had noted increasingly frequent nocturia, hesitancy, diminution in the size of his urinary stream and periodic dysuria. The past history was noncontributory. He specifically denied any cardiorespiratory symptoms.

Physical Examination: The patient was a well developed and well nourished man. The temperature was 36.7° C.; pulse, 85 per minute; respirations, 20 per minute; blood pressure, 150/80 mm. of Hg. The chest was increased in anteroposterior diameter and was hyperresonant, with decreased tactile fremitus and distant breath sounds. The heart was not enlarged and there were no murmurs. The smooth lower margin of the liver was felt 2 to 3 cm. below the right costal margin. The bladder was distended and the prostate gland was reported to be symmetrically enlarged and firm.

Laboratory Data: The initial catheterized urine was grossly bloody, but urine voided on the second hospital day was clear, with a specific gravity of 1.005 and an occasional leukocyte. The red blood cell count was 4,500,000/cu. mm.; white blood

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† This work was done during the tenure of a Research Fellowship of The American Heart Association.

cell count, 14,000/cu. mm., with 80 per cent polymorphonuclear leukocytes. The blood urea nitrogen was 10.5 mg. per cent, and alkaline and acid phosphatase values were normal.

Hospital Course: On the thirteenth hospital day a simple perineal prostatectomy was performed under spinal anesthesia. At no time during the operative procedure did the patient's blood pressure fall. The diagnosis of the pathologist was "adenocarcinoma of the prostate." On the twentieth hospital day a bilateral orchiectomy was performed. The pathologic reports on these specimens were "fibrosis and atrophy of testes, acute and chronic epididymitis with abscess formation." The patient received several courses of penicillin, streptomycin and sulfonamides during and after all operative and instrumentation procedures. His postoperative course was uneventful and he was discharged on August 5, 1950, on maintenance stilbestrol.

Subsequent convalescence was characterized by complete and persistent incontinence controlled with a Cunningham clamp. During urology clinic revisits in August and September the patient was given courses of ammonium chloride and mandelic acid because of persistent pyuria. On October 3, 1950, the patient was referred to the Medical Outpatient Clinic because of pedal edema. At this time the heart was enlarged and there was a regular sinus rhythm with premature beats. No heart murmurs were noted. The patient was digitalized and given mercurial diuretics. On each of two subsequent revisits to the Medical Clinic (October 17 and October 26), the patient's condition was described as "much improved."

Final Admission: On October 30, 1950, the patient was admitted to the hospital in coma. A friend stated that he had been in his usual health until that morning, when he collapsed and fell on the floor.

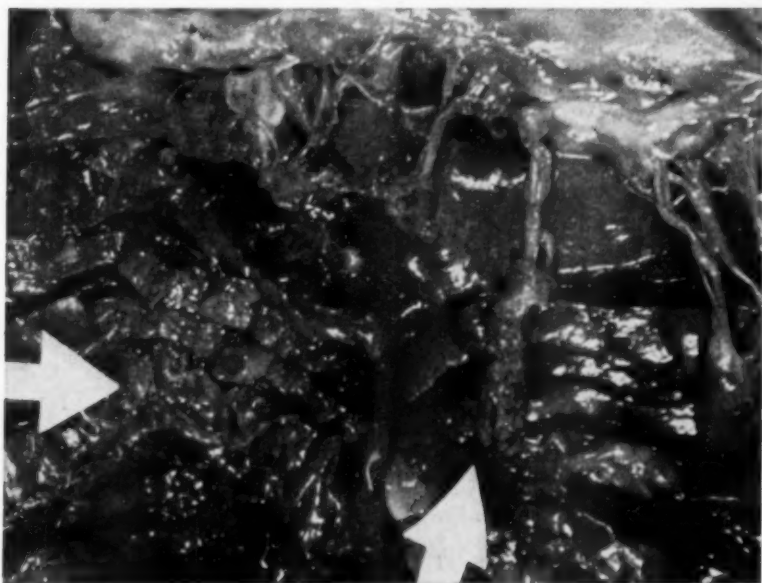


FIG. 1. Left ventricle and mitral valve: the lower arrow indicates the fragmented ruptured anterior papillary muscle, the horizontal arrow its necrotic site of previous attachment.

Physical Examination: The patient was comatose. The temperature was 37.5° C.; pulse, 105 per minute; blood pressure, 86/50 mm. of Hg. There was a complete right flaccid paralysis. The lungs were emphysematous but no râles were heard. The heart was enlarged to the anterior axillary line. There was a systolic thrill at the apex, a harsh, long, systolic murmur over the mitral area, and a soft, aortic systolic murmur. P_2 was greater than A_2 . The rhythm was irregular. The abdomen was not remarkable. The liver was not felt.

Laboratory Data: The urine had a specific gravity of 1.010, 1 plus albumin and 2 to 4 white blood cells per high power field in an uncentrifuged specimen. The white blood cell count was 27,000, with 96 per cent polymorphonuclear leukocytes. The blood urea nitrogen was 71 mg. per cent, the blood creatinine, 3.5 mg. per cent. *E. coli communis* was grown from three blood cultures drawn on separate days.



FIG. 2. Photomicrograph of abscess at margin of ruptured papillary muscle. Hematoxylin and eosin. 105 X.

Hospital Course: The patient was treated with oxygen, penicillin and aureomycin, and Digalen and Thiomerin. His temperature rose to 40.5° C., and he died 47 hours after admission while an electrocardiogram was being taken. Three limb leads were obtained which showed auricular fibrillation and flattening of the T waves. No significant RST or QRS changes were present.

Autopsy Findings: The heart weighed 375 gm. and was of the usual shape but was flabby. The anterior papillary muscle of the left ventricle was found to be detached from the ventricular wall. The ruptured base of the papillary muscle was ragged, friable and necrotic (figure 1). At the site of its former attachment to the left ventricle, the myocardium was similarly necrotic, ragged and friable. Microscopic section of this region of the papillary muscle and left ventricle revealed an abscess

(figure 2) in which gram-negative bacilli were demonstrated. There was a recent mural thrombus attached to the wall of the left ventricle near the site of the papillary muscle rupture. The coronary arteries were only slightly atherosclerotic and their lumens were not significantly narrowed. The remainder of the heart was essentially normal. There were 300 c.c. of slightly hazy fluid in the left hemithorax and 150 c.c. in the right. The lungs were emphysematous and there was a slight bilateral bronchopneumonia. No pulmonary edema was present. There was chronic passive hyperemia of the liver, which weighed 2,150 gm. Ascites and pedal edema were not present. No residual carcinoma was found in several sections taken from the region of the prostatic bed. There was an acute pyelonephritis bilaterally, and a recent small infarct in the left kidney. There was an acute meningitis and a focal encephalitis, and the brain was moderately edematous. In addition, there was a recent infarct of the left insula which involved the fibers of the left external capsule and a portion of the left corona radiata.

Postmortem Bacteriology: Culture of heart's blood, *E. coli communis*; culture of spleen, *E. coli communis*; culture of urine, *E. coli communis*; culture of left lower lobe of lung, *E. coli communis*; culture of pericardial fluid, *E. coli communis* and *Bacillus proteus*; culture of spinal fluid, *E. coli communis*.

Final Pathologic Diagnoses: (1) Focal abscess formation in left ventricle, with necrosis and rupture of left anterior papillary muscle. (2) Acute pyelonephritis. (3) *E. coli* septicemia. (4) Acute meningitis and acute focal encephalitis. (5) Bilateral bronchopneumonia. (6) Mural thrombus, left ventricle. (7) Recent infarct, left insula of brain. (8) Recent infarct, left kidney.

DISCUSSION

The case which is the basis for the present report is the first in which an acute infection has been proved to be the cause of a papillary muscle rupture. The perineal prostatectomy was apparently followed by an acute urinary tract infection due to *E. coli communis*. *E. coli* septicemia resulted in abscess formation in the left ventricle and base of the anterior papillary muscle, with subsequent rupture of that muscle. Gram-negative organisms were demonstrated in the myocardium at the site of the rupture, providing further proof that the myocardial abscess was related to the *E. coli* bacteremia. The recent cerebral and left renal infarcts were probably due to embolization from the recent premortem thrombus which was attached to the wall of the left ventricle. As further sequelae of the *E. coli* bacteremia, there was an acute meningitis, a focal encephalitis and bilateral bronchopneumonia.

In reviewing the 11,550 autopsies done at the Cleveland City Hospital in the 20 years between January 1, 1932, and January 1, 1952, two further cases of papillary muscle rupture were found. One of these, previously reported by Smith,² was the result of an acute myocardial infarct. The other was that of an 83 year old white man who was found to have an acute vegetative endocarditis involving the left anterior papillary muscle. There was an underlying abscess in the papillary muscle which was ruptured. Gram-positive cocci were seen in section of the papillary muscle, but the organisms were not cultured. The coronary arteries were markedly arteriosclerotic, with an old occlusion of the circumflex branch of the left coronary artery. There were, however, no recent occlusions.

The most common cause of papillary muscle rupture is occlusion of a coronary artery with a myocardial infarct affecting the base of the papillary muscle. The

cases of papillary muscle rupture discussed in Askey's report in 1950⁴ were all due to acute myocardial infarction. However, one case was unusual in that the infarction resulted from periarteritis nodosa which involved the coronary arteries. Several cases of papillary muscle rupture have also been reported following blunt injury to the chest. In 1920 Kleberger⁵ reported the case of a soldier whose thorax was contused following a hand grenade blast. No ribs were fractured, and the outside of the heart had only a few epicardial hemorrhages. The anterior papillary muscle of the right ventricle was torn longitudinally but was not completely detached. The posterior papillary muscle of the right ventricle was also torn and was attached to the wall of the heart by only a very few thin strands. In the case reported by Payne and Hardy,⁷ as well as the one reported by Glendy and White,⁸ there was a contusion of the left ventricle with rupture of the anterior papillary muscle. A third cause of papillary muscle rupture is infection of the myocardium. The only well substantiated case is the one reported by Spalding and von Glahn.⁹ In this instance a 31 year old Negro male with a 4 plus Wassermann reaction died suddenly during a recurrent episode of congestive failure. The left posterior papillary muscle was ruptured. Microscopic examination showed a central focus of "coagulative necrosis" surrounded by leukocytes. Spirochetes could be demonstrated in a Levaditi preparation of the ruptured end of the papillary muscle. The first reported case of papillary muscle rupture, that of Merat in 1803,¹⁰ may have been due to a similar luetic lesion, since the patient had an aneurysm of the aorta. Two early cases were possibly due to infection, although this was not proved. In 1824 Bertin¹¹ presented the case of a 22 year old tuberculous girl who died of a rupture of the papillary muscle of the right ventricle, allegedly due to tuberculous vegetations. In the case reported by Spanton in 1865¹² there was a ruptured right papillary muscle in a 23 year old woman which was said to be secondary to vegetations on the valves and chordae tendineae. The patient had a pelvic inflammatory disease, and her uterus was described as being "surrounded by pus and the ovaries full of it."

Schwartz³ has pointed out the fact that pulmonary edema is a common accompaniment of papillary muscle rupture when the basis of the rupture is a myocardial infarct. In this regard he quoted experimental work by Wiggers and Feil,¹³ who produced mitral insufficiency in dogs. They found that the normal left auricle could accommodate the increased volume of blood during systolic ejection with no "back pressure" effects on the pulmonary artery or right heart. However, when systemic arterial resistance was increased, there was a "damming back" of blood into the pulmonary artery and right heart. It was concluded by Schwartz that "as long as the left ventricle is functionally competent, no pulmonary edema should be produced." In the present case, the coronary arteries and the myocardium as a whole were relatively normal, and there was no evidence of pulmonary edema.

Askey⁴ found that a systolic thrill is common in rupture of the interventricular septum but was absent "in every instance of ruptured papillary muscle." He felt that this was an important differential point and stated that "if a thrill is associated with the murmur, a ruptured papillary muscle is unlikely." Since a very prominent apical systolic thrill was noted in the present case, this criterion must be considered of less significance than was previously thought.

Reports of myocardial abscesses are not common. However, Saphir¹⁴ states that there "seems to be no question that such abscesses occur quite often." He found 32 cases of abscesses of the heart out of 5,626 consecutive autopsies, an incidence of 0.2 per cent. The bacteriologic agent in the great majority of cases is *Staphylococcus aureus*,^{15 and 16} with septicemia usually following a bacterial endocarditis or acute osteomyelitis. Gladden¹⁷ reported a case of cardiac rupture due to a *Staphylococcus aureus* abscess of the heart which was secondary to an acute infection of the knee, and he reviewed the eight cases of myocardial abscess with rupture previously recorded in the literature. The present case most closely resembles the one recently reported by Miller and Edwards.¹⁸ In their case a myocardial abscess superimposed on an acute myocardial infarct was apparently caused by an acute pyelonephritis. *E. coli* was cultured from the pelvis of the right kidney and from the left ventricle, and gram-negative bacilli were observed in the myocardial abscess.

SUMMARY

A case is presented in which an *E. coli* septicemia following acute pyelonephritis resulted in a myocardial abscess and rupture of the left anterior papillary muscle. This is the first such case to be reported. Reference is made to a second case of abscess and rupture of the left anterior papillary muscle secondary to an acute vegetative endocarditis.

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VARICELLA PNEUMONIA WITH SHOCK AND HEART FAILURE*

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CHICKENPOX usually runs a benign course, but it has not been generally appreciated that it may be a severe disease, especially in adults. The virus is widely disseminated throughout the body, but only rarely does it produce visceral manifestations such as pneumonia, encephalitis and nephritis. The following case report illustrates a most malignant form of varicella pneumonia, with severe cardiopulmonary complications.

CASE REPORT

A 36 year old white male was admitted to Barnes Hospital on February 10, 1952. Sixteen days before admission one of his children had developed a typical varicella eruption. Four days before admission the patient developed fever and a little malaise. On the second day of his illness his first chickenpox rash appeared on the upper abdomen, and extended in successive crops over the trunk, face, scalp and proximal portions of the extremities. At this time he noted a sharp sticking pain in the right lower chest, but there were no abnormal physical findings. He was started on 1 gm. of aureomycin daily. During the third day of illness he felt better, but on the following day (the day before admission) he became dyspneic and developed a fever of 38.8° C. He looked toxic and apprehensive and his respirations were rapid, but his lungs were clear and his color was good. There were chickenpox lesions in his left conjunctiva and in his mouth, but not in the pharynx. On the morning of admission his temperature reached 40° C. and dyspnea increased. A slight, nonproductive cough developed. When seen at home he was intensely cyanotic and appeared moribund, with a respiratory rate of 65 per minute and unobtainable radial pulse and blood pressure. He was immediately given intravenous Coramine and epinephrine, and oxygen by mask. When nor-epinephrine could be obtained, intravenous infusion of this in a concentration of 0.4 mg. per liter restored his blood pressure to a level of 90 to 100 systolic. He was transported to the hospital in this condition. It should be noted that his wife was being treated at home during this period for a virus pneumonia, and his second child developed typical chickenpox on the day of the patient's admission to hospital.

Pertinent past history included bilateral pleurisy in 1937 following appendectomy, and possible rheumatic fever at the age of five years for which he was kept at bed-rest for three months. He was, however, on active Navy duty in World War II.

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His last smallpox vaccination was in December, 1950, and an immune reaction was observed. He had no history of chickenpox.

The physical examination on admission showed a temperature of 40° C. rectally; pulse rate, 152; respiratory rate, 58; blood pressure, 106/70 mm. of Hg. The patient was a well developed man, delirious and extremely agitated, moving all extremities in response to painful stimulation. Skin and mucous membranes were deeply cyanotic. An extensive, typical varicella eruption in various stages of development was present. The rash was most extensive on the scalp and face, trunk and proximal portions of the extremities, but a few lesions were present on the palms and soles, conjunctiva, buccal membranes, palate and posterior pharynx. After oxygen therapy, hypoactive equal reflexes were obtained in the arms and ankles. Knee jerks were absent. Equivocal Babinski's sign and Gordon's and Oppenheim's signs were present on the left. The remainder of the physical examination was normal.

Laboratory data on admission: Blood counts and chemical findings are summarized in figure 1. Urinalysis had a specific gravity of 1.026, pH of 6.0, trace of albumin, negative sugar, many hyaline and granular casts, and a few white blood cells. Cardiolipin test was negative. Blood culture was sterile. Sputum culture showed usual mixed flora. CO₂ combining power was 26 mEq. per liter.

Only with continuous intravenous nor-epinephrine was his blood pressure maintained at 110/70 mm. of Hg. With mask oxygen, cyanosis was less marked. Five hours after admission he was more responsive, but then he coughed up approximately 150 c.c. of bright red blood, some mixed with sputum. Numerous fine râles were heard over both lower lobes for the first time. Intramuscular treatment with 2,400,000 units of penicillin and 2 gm. of streptomycin daily was started.

Early in the morning of the second hospital day, eight hours after admission, he was started on large doses of aqueous adrenal cortical extract intravenously. Seven hours later intramuscular cortisone was added to the therapy. Total daily dosage is indicated in figure 1. Because the serum proteins were low, 500 c.c. of plasma were given intravenously. Thrombocytopenia (figure 1) was also discovered, but bleeding time was six minutes; prothrombin time was 65 per cent of normal. At 3 p.m. on the second day a nodal tachycardia was noted (February 11, figure 2) which spontaneously reverted to a sinus mechanism by 11 p.m. By evening of the second day his peripheral circulation had improved so that nor-epinephrine could be discontinued. The skin was pinker and the red areola around each chickenpox lesion was evident. Marked dyspnea and tachypnea persisted, and there were increasing numbers of medium and fine râles over both lung fields, with transient areas of bronchovesicular breathing at the bases. Portable roentgenograms of the chest taken at this time (figure 3A) showed an extensive diffuse, nodular infiltration, confluent in many areas.

Early on the third hospital day the patient again developed peripheral circulatory collapse. Intravenous nor-epinephrine was again administered and was continued for 24 hours. Additional plasma and salt-free albumin were given intravenously, and 16 c.c. of human gamma globulin were administered intramuscularly. Aminophylline was given by intravenous infusion because of continued dyspnea. Urinary output was good, and renal function improved.

On the fourth hospital day the patient was afebrile but still dyspneic and cyanotic. His liver was palpated two fingerbreadths below the right costal margin; there were fewer râles in his lungs. During that evening and the morning of the next day, the pulse rate rose to 120 per minute. A second portable roentgenogram of the chest (figure 3B) showed slight clearing of the diffuse nodular infiltration. Venous pressure at this time was 155 mm. of saline; Decholin circulation time was 10 seconds. During the next three hours the patient became increasingly dyspneic, orthopneic and cyanotic despite continued oxygen by mask. His neck veins became markedly distended, but there was no increase in râles in the chest. Electrocardiogram (Feb-

ruary 14, figure 2) showed slight prolongation of intraventricular conduction, the appearance of a prominent S₁ and Q₁, a smaller Q in Leads II and aVF, ST elevation and T wave inversion in III, and an RR¹ pattern in V₁. Venous pressure rose to 263 mm. saline. He was immediately given 1.6 mg. of Cedilanid and 250 mg. of aminophylline intravenously. In two and one-half hours he was less dyspneic and cyanotic, and his neck veins were less distended. Venous pressure had fallen to 110 mm. of saline. Adrenal extract and cortisone therapy were discontinued at this time.

The patient continued to have evening fever. On the sixth hospital day he was euphoric and hallucinating periodically. Venous pressure that morning was 175 mm.

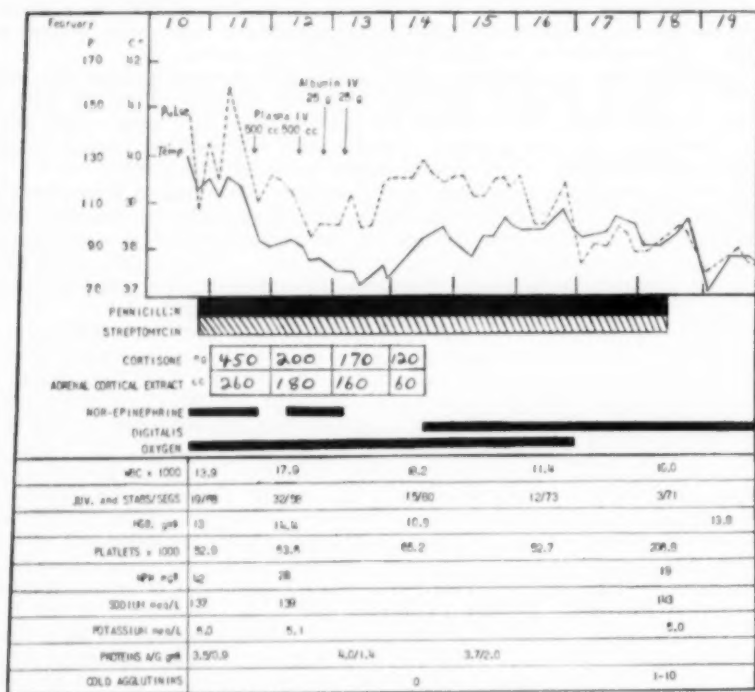


FIG. 1. Temperature and pulse graphic, and principal therapeutic agents for the first 10 days in the hospital. On February 14 there were two nucleated RBC per 100 WBC. Reticulocyte count was 0.9 per cent and Coombs test was negative. Icteric index and liver function were normal. Note that upper normal NPN for this laboratory is 25 mg. per cent.

of saline. Five hundred milligrams of aminophylline given intravenously produced no change. Digitalization was maintained with full doses of oral digitoxin. Venous pressures on the seventh and eighth hospital days were 165 and 135 mm. of saline. Electrocardiogram on February 16 (the seventh hospital day) is shown in figure 2.

A left anterior pleural friction rub was heard on the sixth hospital day. Two days later a to-and-fro friction rub, interpreted as a pleuropericardial sound, was heard in the same area. On this day the patient became more alert and rational; he was also afebrile, and respirations slowed to about 24 a minute without oxygen.

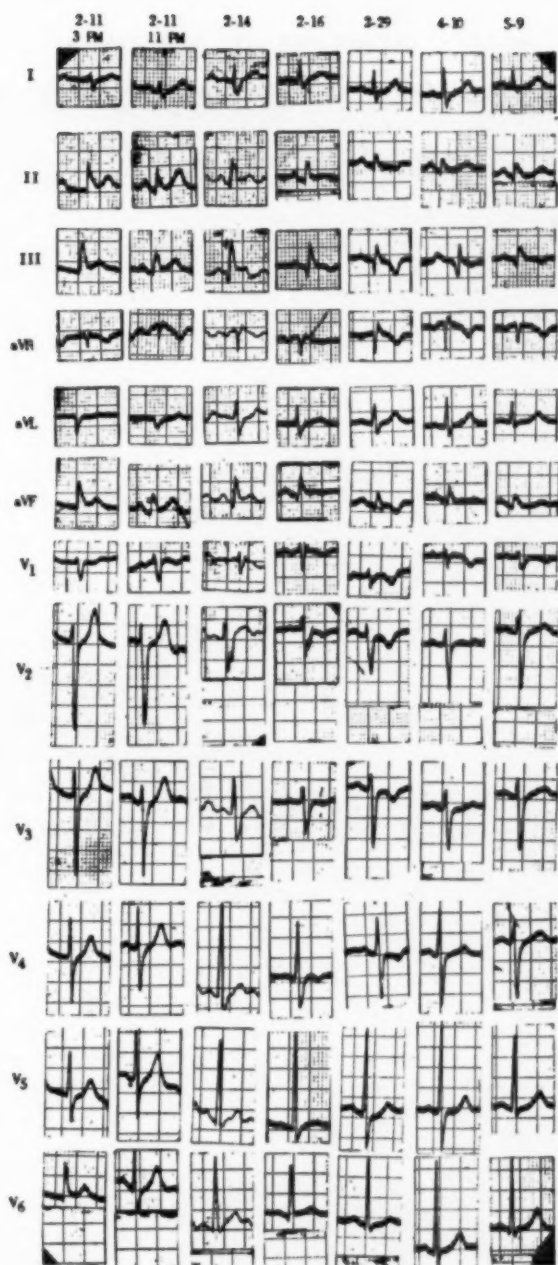


FIG. 2. Serial electrocardiograms on the dates as indicated above each vertical column. Note that digitalis was begun after the electrocardiogram on February 14, the fifth hospital day, and discontinued on February 27, the eighteenth hospital day.

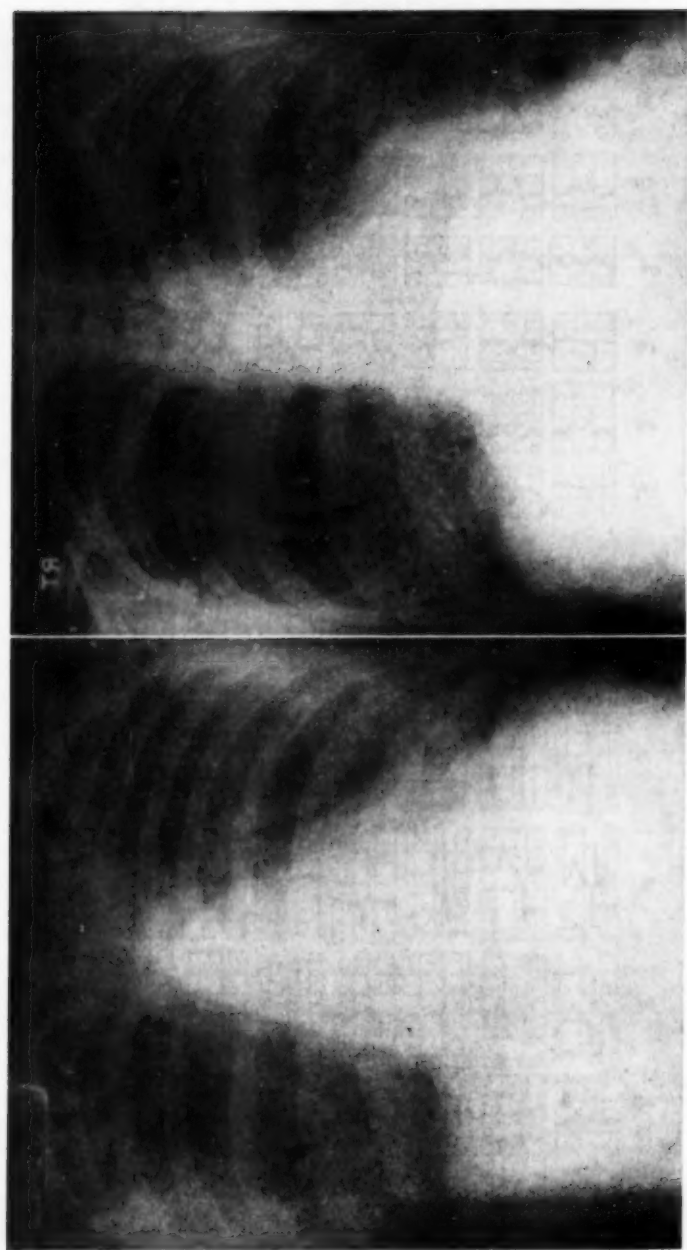


FIG. 3. A. Portable AP x-ray of the chest on the second hospital day. Note the extensive diffuse nodular infiltration in all lung fields. B. Considerable clearing of the nodular infiltration is present on the fifth hospital day.

On the ninth hospital day a diffuse, maculopapular drug rash appeared on the entire trunk, so antibiotics were discontinued. With antihistaminic therapy the rash faded in a few days. The superficial veins in both arms used for intravenous infusions became thrombosed about the time the platelet count began to rise.

On the thirteenth hospital day a left homonymous hemianopsia was discovered. (Visual fields at the time of discharge from the hospital showed that there was macular sparing and a thin rim of vision remaining at the periphery.) Neurologic examination was otherwise normal. A standard chest film on the fourteenth hospital day (figure 4A) showed a further diminution in the diffuse nodular infiltration. The heart was of normal size. The patient continued to improve and was eating well, although a tachycardia of 90, slight leukocytosis and a few râles at the right base persisted.

On the eighteenth hospital day digitoxin was discontinued. The next day he complained of pain without swelling in the right axilla. During the following evening he complained of gaslike pains in the epigastrium and lower substernal region which lasted intermittently all night. Electrocardiogram then (February 29, figure 2) showed T waves more inverted in several leads. White blood cells and differential were normal. Temperature was 37.8° C. The twenty-second hospital day he had pleurisy in the right chest, then in the left. Temperature spiked to 39.4° C. without rigor; there were râles in both bases. White blood cell count was 19,250; blood culture was sterile. He had no cough or sputum then or at any time during this pulmonary complication. He was treated with full therapeutic doses of chloromycetin, heparin and Dicumarol. The following day there were friction rubs and signs of consolidation at both bases, confirmed by roentgenogram of the chest (figure 4B). Large doses of penicillin and streptomycin were added to the previous therapy. Gradually diminishing fever, right pleurisy and leukocytosis persisted for three weeks, with the transient occurrence of a few myelocytes and metamyelocytes in the differential white count. On the thirty-fourth hospital day a chest film (figure 5A) showed an area of rarefaction in the right lower lobe consolidation. This and a similar area in the left lung were found on laminagrams (figure 5B). One week later the rarefaction had virtually disappeared (figure 6A).

Antibiotics and anticoagulants were discontinued on the fifty-second day, except that oral penicillin was given for one more week. The patient was ambulated gradually and was discharged from the hospital on the sixty-third day. Physical examination of the chest was normal. Vital capacity was 3 L., blood counts were normal, and the electrocardiogram had improved (April 10, figure 2).

During the first month at home he had no pulmonary symptoms and continued to gain in weight and strength. The left hemianopsia was unchanged. On May 9, after four weeks at home, electrocardiogram (figure 2) now showed all T waves to be normal. Roentgenogram of the chest (figure 6B) showed a scar in the right lower lobe and considerable clearing of the diffuse interstitial pneumonitis. During the next three months of follow-up he continued to improve and there were no further changes in the electrocardiogram or chest roentgenogram.

DISCUSSION

In the days prior to modern chemotherapy Bullowa and Wishik¹ reported 21 cases of pneumonia complicating 2,534 cases of chickenpox, an incidence of 0.8 per cent. However, these were due to complicating bacterial infections, usually *Streptococcus angiosus*, and in eight fatal cases there were predominantly polymorphonuclear leukocytes and bacteria in the alveoli.²

In 1942, Waring, Neuburger and Geever³ first presented detailed reports of two adult patients with varicella pneumonia, one of whom died. There have

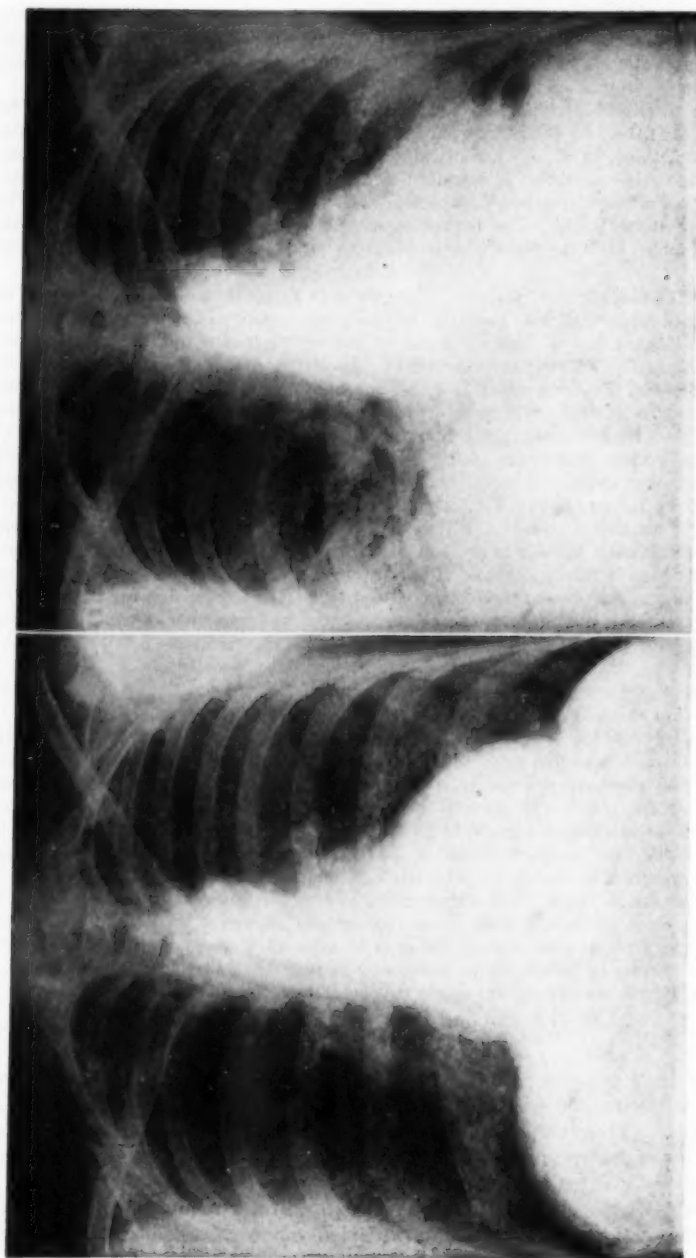


FIG. 4. A. Standard six foot PA chest x-ray on the twenty-third hospital day, showing further diminution in the nodular infiltration. B. Standard chest x-ray on the fourteenth hospital day, showing consolidation in portions of both lower lobes.

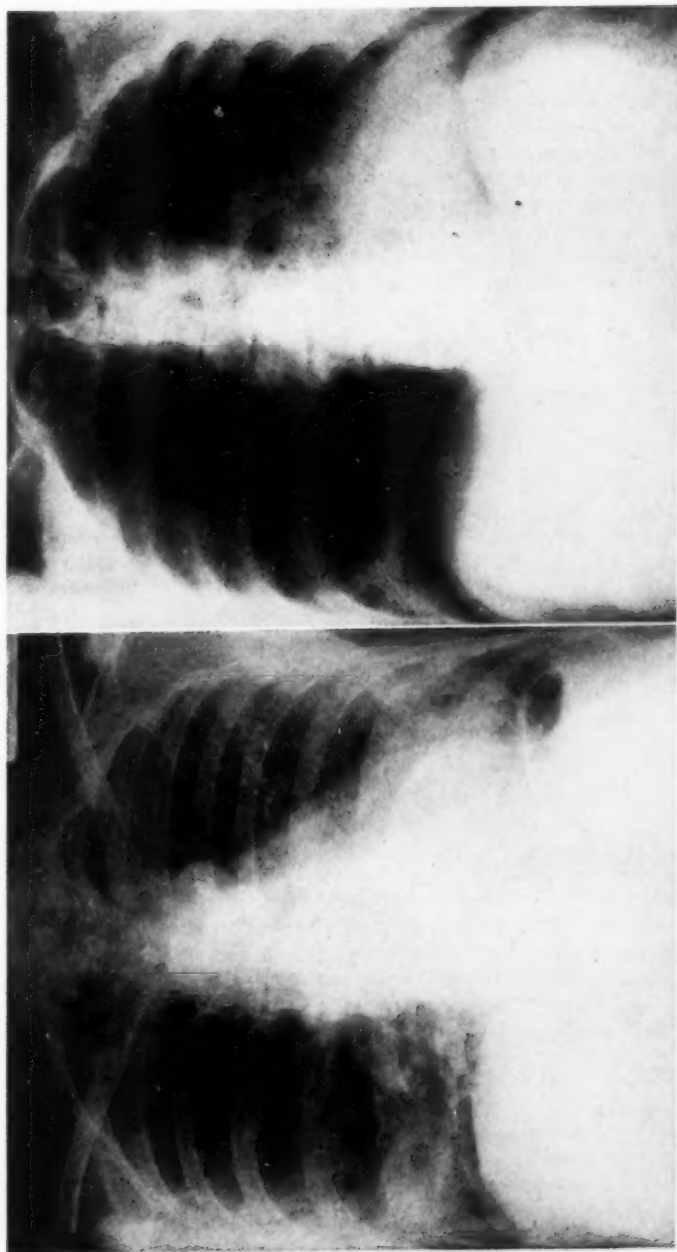


FIG. 5. A. Chest x-ray on the thirty-fourth hospital day, showing clearing of the right lower lobe consolidation, with a suggestion of rarefaction in it. B. AP laminagram of the chest on this date at 8 cm. from the film, defining the area of rarefaction, which measured $1\frac{1}{2}$ by 3 cm. and showed a similar smaller area in the left midlung field.

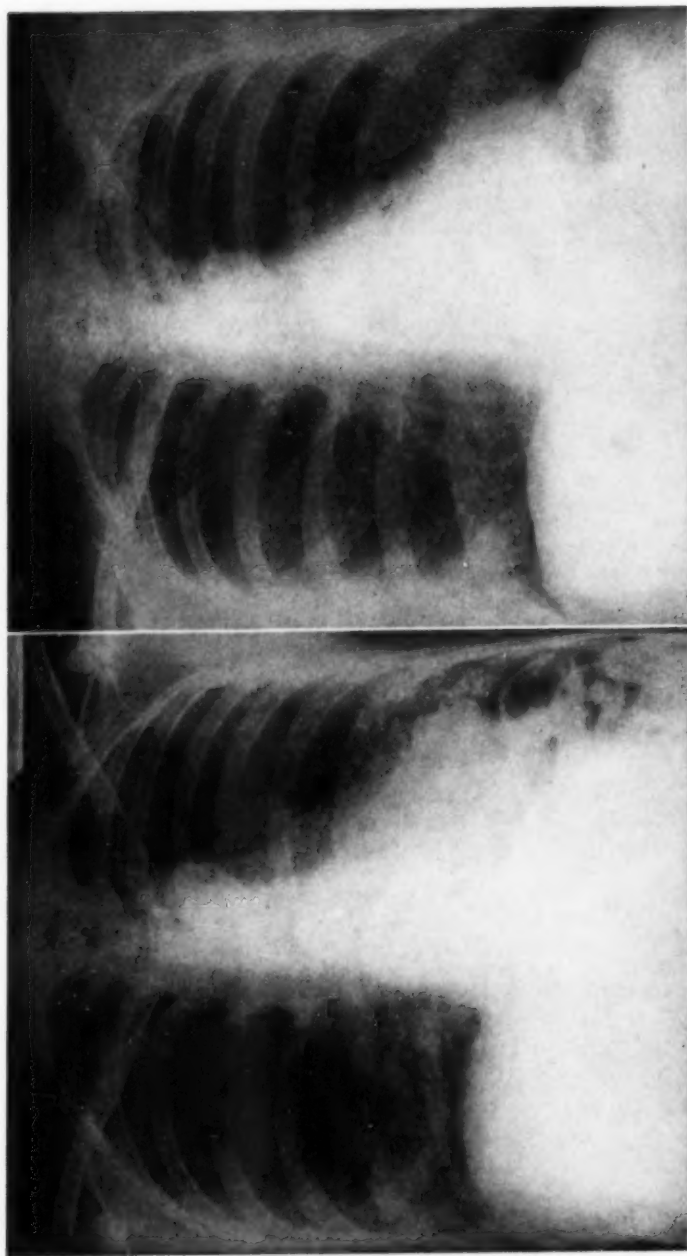


FIG. 6. A. Standard chest x-ray on the forty-first hospital day, showing virtual disappearance of the rarefaction in the right lower lobe. B. Chest x-ray on May 9, after four weeks at home, showing a scar in the right lower lobe and considerable clearing of the diffuse nodular infiltration in all lobes of the lung.

been nine additional cases reported with this condition,³⁻¹⁰ the present one included. The main clinical features are summarized in table 1. The similarity in their clinical course is striking. In all cases there occurred an alarmingly rapid onset of dyspnea and tachypnea, fever and cough within two to six days of the first appearance of the chickenpox rash. Gross hemoptysis, usually several ounces, occurred in six of the 11 cases. The patients were all cyanotic, with marked tachycardia. Vasomotor collapse occurred in three cases, two of them fatal. There were many moist râles scattered throughout the lung fields, with transient areas of bronchovesicular and bronchial breathing. In several cases the symptoms of pulmonary complication preceded physical signs by several hours, especially in our case, where medical shock existed for 10 hours prior to appearance of râles. Pleurisy occurred in four patients. Three patients were digitalized, but only in the present report was there detailed evidence of heart failure. White blood counts ranged from 4,000 to 14,000, with slight left shifts in the differential. The potential bacterial pathogens present in a few of the sputa were treated early with adequate chemotherapy, and blood cultures, when taken, were sterile. Roentgenograms of the chest uniformly showed a diffuse nodular type of pneumonic infiltration. The findings slowly resolved over a period of several weeks.

Detailed postmortem observations are available in the four fatal cases.^{2, 6, 7, 10} The changes found in all the lungs were similar to those seen in other types of virus pneumonia. Features consistently noted were swelling, proliferation and desquamation of the septal cells to form large mononuclear phagocytes which form the usual cellular exudate. Alveoli were lined with hyaline membranes. Foci of necrosis, hemorrhage, fibrinous exudation and arteriolitis were found in many areas. Bacteria and polymorphonuclear leukocytes were rare. In two cases^{7, 10} characteristic type A intranuclear inclusion bodies of varicella were found in alveolar septal cells and macrophages, and in bronchiolar epithelial cells. These inclusion bodies were also observed in the spleen, liver, adrenals, tracheo-bronchial lymph nodes, the epidermis, and in fibroblasts and endothelial cells of the dermis and subcutaneous tissues in one case.¹⁰ Chickenpox has been noted on the surfaces of the pleura,^{4, 10} liver and spleen.⁴ A toxic encephalitis and nephrosis were present in Waring's case,² and sarcoidosis was a complicating disease in Eisenbud's case.¹⁰

It is of interest that in the reported cases of congenital chickenpox,¹¹ disseminated foci of necrosis containing intranuclear inclusion bodies were found in the lungs, liver, spleen, pancreas, adrenals, kidney, thymus and the gastrointestinal tract.

The rare neurologic complications of chickenpox have been reviewed by Underwood¹² under the headings of prodromal convulsions, meningoencephalitis, encephalomyelitis, polyneuritis and ocular changes. The agitated delirium and neurologic manifestations present in our case on admission to the hospital could be accounted for on the basis of shock and anoxia. The euphoria and hallucinations later on in his course are more suggestive of encephalitis; however, hemianopsia or other visual field defects are not mentioned by Underwood. We can speculate that this patient's persistent left hemianopsia with macular sparing is due to an area of encephalomalacia involving the right optic radiation within the temporal lobe or occipital cortex. The cause of this softening may have been either encephalomyelitis or vascular occlusion during shock.

TABLE I

Authors, Year and Reference	Age and Sex	Number of Days from First Rash to Pulmonary Symptoms	Respiratory Rate	Pulse Rate	Hemoptysis	Cyanosis	Physical Signs of Diffuse Bronchopneumonia	Diffuse Nodular Infiltration on X-ray	White Blood Count	Bacteriology of		Chemotherapy	Complications
										Sputum	Blood Culture		
Waring, Neuburger and Geeser ^b 1942	40M	4	32	140	+	+	+	+	15,250	Type 18 Pneumococcus from mouse only		Sulfathiazole	Encephalitis Delirium Death
Case 2	33M	5	48	160	+	+	+	+	8,800	<i>Streptococcus anginosus</i>		Sulfathiazole Sulfanilamide	Azotemia Digitalized Pleurisy Osteomyelitis of jaw
Rausch, Grable and Musser ^a 1943	27M	4	rapid	rapid	0	+	+	+	6,200	No pneumococci		Sulfathiazole	Laryngospasm Pleurisy
Claudy ^a 1947	32F	3	60	160	+	+	+	+	9,200	Few type 4 pneumococcus		Sulfadiazine	Shock Azotemia Digitalized Death
Grayson and Bradley ^a 1947	34M	2	rapid	rapid	0	+	+	+	4,000	Normal flora		Sulfadiazine Penicillin	Nephritis
Wesselhoef and Pearson ^a 1950	46M	4	40	120	0	+	+	+	10,400	Alpha hemolytic streptococcus		Penicillin Streptomycin	Unilateral orchitis with atrophy

TABLE 1—Continued

Authors, Year and Reference	Age and Sex	Number of Days from First Rash to Pulmonary Symptoms	Respiratory Rate	Pulse Rate	Hemoglobin Gals	Cyanosis	Physical Signs of Diffuse Bronchopneumonia	Diffuse Nodular Infiltration on X-ray	White Blood Count	Bacteriology of Sputum		Chemotherapy	Complications
										Blood Culture			
Frank ⁷ 1950	34F	4	rapid	rapid	+	+	•	•	•	•		Penicillin	Death
Bunn and Hammond ⁸ 1950	30F	4	50	140	0	+	+	+	10,050	No growth		Penicillin Streptomycin Aureomycin	6 months pregnant
										Blood sterile			
Michel, Coleman and Kirby ⁹ 1951	27M	3	44	88	+	+	+	+	6,300	<i>Streptococcus viridans</i> Mouse negative		Aureomycin	None
										Blood sterile			
Eisenbud ¹⁰ 1952	71F	6 (approx.)	32	132	0	+	+	•	14,400	<i>Streptococcus viridans</i> <i>Staphylococcus albus</i>		Terramycin	Sarcoidosis Azotemia Shock Pleurisy Death
										Blood sterile			
This report	36M	3	65	152	+	+	+	+	13,850	Few <i>Staphylococcus albus</i> and <i>S. aureus</i>		Aureomycin Penicillin Streptomycin Chloromycetin	See text
										Blood sterile			

• = Not described.

The thrombocytopenia which our patient had was not of major clinical significance because his rash was never hemorrhagic, there were no bleeding points except in the lungs, and his bleeding time was normal. Cohen and Banemer¹³ described a case of hemorrhagic chickenpox in an 11 year old boy with multiple bleeding sites, and with all the hematologic manifestations, including bone marrow findings, of idiopathic thrombocytopenic purpura.

The initial and critical complication of this case was the profound and prolonged shock with delirium, fever and anoxia. This medical shock was presumably due to viremia itself or to the toxic reaction of extensive virus infection. The demonstration of varicella inclusion bodies in vascular endothelium suggests widespread vascular damage due directly to the virus. As noted previously, the foci of necrosis due to varicella have been found in the adrenal cortex.¹¹ Rich¹⁴ believes that necrosis of isolated cells in the adrenal cortex initiates a striking tubular-like transformation which may be etiologically related to the circulatory collapse of severe acute infections. The anatomic basis for acute adrenocortical insufficiency or exhaustion in this patient was not clinically important, but the survival from acute adrenal failure depends on massive substitution therapy.¹⁵

The emergency use of nor-epinephrine in intravenous fluids raised the blood pressure and radial pulse to perceptible levels and permitted removal of the patient to the hospital by ambulance, but the continued use of nor-epinephrine did not remove the critical aspect of the patient's condition. Cyanosis increased in spite of oxygen mask, and massive doses of aqueous adrenocortical extract were started intravenously, which experienced endocrinologists^{15, 16, 17} advise in Waterhouse-Friderichsen syndrome. In addition, cortisone, 450 mg. the first day and 200 mg. the second day, was given as sustaining corticoid replacement. These doses, though large, were well tolerated, and approximate the 300 mg. per day dose which affords maximal adrenal corticoid replacement therapy.¹⁸ It is interesting to note that the serum electrolytes remained normal during this intensive adrenocortical hormone therapy.

The severe shock seemed sufficient justification for the addition of cortisone, in spite of the adverse effects of cortisone on experimental virus infections.^{19, 20} Other measures in the treatment of the medical shock of this patient were oxygen by plastic mask plus an oxygen tent.* This combination effectively lessened the initial cyanosis and was continued for five days. The correction of low serum proteins by plasma and salt-free albumin may have been helpful during the period of acute collapse and hemoconcentration.

The precipitous onset of heart failure on the fifth hospital day was manifested by increasing tachycardia, dyspnea, orthopnea, cyanosis and a rapidly rising venous pressure. This complication occurred at a time when the lungs were clearing of râles, and the chest x-ray (figure 3B) showed less parenchymal infiltration. The clinical picture suggested acute cor pulmonale, and the electrocardiographic changes, including ST segment elevation in Lead III, on that day (February 14) were consistent with those described as characteristic of right ventricular strain.^{21, 22} However, Murnaghan, McGinn and White²² noted that such changes, when due to cor pulmonale, rarely last longer than a week. The presence of a small Q wave and elevated S-T segment in Lead aVF on February

* Suggested by Dr. D. Eastwood, Assistant Professor of Anesthesiology in Washington University School of Medicine.

14, maximal T wave inversions in many leads on February 29, and only gradual return to a virtual normal pattern by May 9 (figure 2) speaks for the presence of a superimposed myocardial disease, particularly posterior myocardial damage or infarction. Currens,²³ in careful postmortem studies of 30 cases of pulmonary embolism, found a recent myocardial infarction without coronary thrombosis in four of them. Our patient's initial prolonged state of shock favors this possibility. Myocarditis and/or pericarditis associated with chickenpox is another possibility, although these have not been described in the few fatal cases reported to date.

A precedent for the occurrence of acute cor pulmonale in acute pneumonia is difficult to find. In fact, White,²⁴ in his monograph, *Heart Disease*, states: "Pneumonia and other pulmonary infections do not give rise to acute cor pulmonale." Mack, Harris and Katz²⁵ describe the case of a 21 year old woman with pulmonary tuberculosis in whom electrocardiographic changes of acute cor pulmonale developed with a terminal lobar pneumonia. There were no pulmonary emboli at autopsy.

The acute cor pulmonale in our patient may have been due to at least two factors. The first was the extensive, diffuse interstitial pneumonia with arteriolitis, providing an anatomic basis for pulmonary arteriolar obstruction; the second was the marked hypoxia. Short-term hypoxia in human subjects has been shown to cause considerable pulmonary hypertension due to pulmonary arteriolar vasoconstriction.²⁶ The value of digitalis in acute cor pulmonale has been a debatable subject; however, its use is recommended by White.²⁴ The fall in venous pressure and rapid improvement on February 14, which our patient experienced within three hours, were undoubtedly attributable to digitalis, since intravenous aminophylline had caused no reduction in venous pressure on two previous occasions.

The actual events of the late pulmonary complications of this patient's illness can only be conjectured. It is presumed that he had pulmonary embolism with infarction, and/or secondary pneumonia, the source of his emboli being either the upper extremity thrombosis or intracardiac thrombosis. It is admitted, however, that he failed to exhibit some of the cardinal features of pulmonary embolism. While the massive doses of antibiotics may have masked some of the clinical features, his course, without cough or sputum, was not that expected of lung abscess. It is suggested that an aputrid pulmonary necrosis²⁷ accounted for the areas of rarefaction noted relatively briefly in both lungs.

The failure of aureomycin in doses of 1 gm. a day for the two days prior to our patient's collapse confirms the impression that varicella virus is not affected by this antibiotic.^{8, 28} Two authors, however, have reported that aureomycin may shorten the course of varicella pneumonia.^{8, 9}

SUMMARY

A case is reported of severe chickenpox in a 36 year old male with extensive pneumonia and complicating shock, heart failure, homonymous hemianopsia and pulmonary suppuration. The clinical features of the pneumonia, presumably due to varicella virus, are consistent with those described in previously published cases. The pathogenesis and therapy of the patient's shock are discussed. Evidence is presented that heart failure occurred as a result of acute cor pul-

monale; dramatic improvement followed the administration of intravenous digitalis.

ADDENDUM

Since this paper was accepted for publication, another report has appeared of three adult patients with varicella pneumonia, uncomplicated by shock or heart failure.²⁸ These patients all presented the typical clinical and roentgenographic features reviewed in this paper, and all underwent complete recovery in two to three weeks.

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XANTHOMATOUS BILIARY CIRRHOSIS *

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THE occurrence of cutaneous xanthomatous lesions and hyperlipemia in the presence of hepatic dysfunction has only recently been recognized as a single clinical entity. First in 1937 Thannhauser and Magendantz,¹⁰ and later in 1940 Thannhauser¹¹ described and correlated this combination and called it "xanthomatous biliary cirrhosis." Since that time there have been only about 30 cases with autopsy reported in the medical literature.

It is the purpose of this paper to report one additional necropsied case, and to include a very brief review of the clinical and pathologic picture of this disease.

CASE REPORT

The patient was a 36 year old white female first seen by us (H.M.P.) at the University of Michigan Hospital on June 20, 1944. At that time her chief complaint was jaundice, which had appeared insidiously four months previously, without pain, swelling, fever or gastrointestinal symptoms. The jaundice had been followed in several weeks by generalized pruritus. The icterus had been increasing in severity since the time of onset. Two months before being seen she reported the appearance of flat yellow plaques in the palmar creases and, later, over the face. Associated were numerous flat-topped yellow papules which erupted over the tips of the fingers, thorax and face. There had been a loss of 10 pounds in body weight.

There was a family history of diabetes in the patient's mother and a sister. Her past medical history was negative. She had had a moderate alcoholic intake for 16 years, but was by no means a chronic alcoholic.

Physical examination showed the patient to be an asthenic white female, somewhat undernourished, but not acutely ill. The temperature was 100° F.; pulse, 106;

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From the Department of Internal Medicine, University of Michigan Hospital, University of Michigan, Ann Arbor.

respiratory rate, 18; blood pressure, 9/50 mm. of Hg, right arm, recumbent. The skin was definitely jaundiced. There were two types of lesions present on the skin: (1) a plaquelike intradermal accumulation of yellowish deposits over the palms and antecubital spaces, axilla, neck, face and eyelids, and (2) papular, flat-topped lesions over the cheeks, chin, finger tips, shoulders and breasts. The liver was 7 cm. below the right costal margin, and the splenic tip was rather easily palpable on deep inspiration.



FIG. 1. View of tuberous xanthoma lesions on face.

Laboratory studies revealed a hemoglobin of 66 per cent, or 10.3 gm., a red blood cell count of 4.4 million per cubic millimeter, and a white count of 9,000 per cubic millimeter with a normal differential. Glucose tolerance test after a three day period of high carbohydrate diet was as follows: fasting, 64 mg. per cent; one hour, 133 mg. per cent; one and one-half hours, 100 mg. per cent; two hours, 87 mg. per cent; two and one-half hours, 72 mg. per cent; three hours, 62 mg. per cent; three and one-half hours, 39 mg. per cent; four hours, 44 mg. per cent. The hippuric acid was normal.

Urinalysis on repeated occasions failed to show urobilinogen present in dilution of over 1 to 10. Stools were intermittently acholic; there were frequent afternoon elevations of temperature to 100° F. The gallbladder was not visualized by cholecystogram, and there was no evidence of opaque stones. Upper gastrointestinal x-ray series was normal. Total serum proteins were 7.5 mg. per cent; albumin, 3.3 mg. per cent; globulin, 4.2 mg. per cent; bilirubin, 4.5 mg. per cent.

The patient was placed on a medical régime consisting of a high protein, high carbohydrate, low fat diet, choline, brewer's yeast, inositol, ferrous sulfate and vitamin K. Later she was given a cholesterol-free diet. Neither program seemed to cause any improvement over a six month period. During one hospital admission she had four phlebotomies of 500 c.c. each, with replacement of the cells after careful washing. The hemoglobin before this procedure was 75 per cent, or 11.7 gm., and serum cholesterol was 1,300 mg. per cent. Similar determinations following autotransfusion showed a hemoglobin of 83 per cent, or 12.9 gm., and cholesterol of 625 mg. per cent. The fall in cholesterol, however, was not permanent. At this time total serum



FIG. 2. Multiple papular, flat-topped and planum lesions which appeared on hands early in course of disease and remained unchanged until death.

proteins were reported as 9.1 per cent; albumin, 4.0; globulin, 5.1 per cent, with an A/G ratio of 0.78.

In February, 1945, a choledochostomy was performed and a T-tube was held in place for a period of four months, at which time her cholesterol had fallen from 1,070 mg. per cent to 600 mg. per cent. There was still no change in her general condition or appearance, and she was again placed on the medical program mentioned above. She was followed as an out-patient for the next two years, during which time the course was progressively downward.

Because of her continued high cholesterol values, even with a basal metabolism rate of plus 8 per cent, she was treated with desiccated thyroid (gr. 1.5) daily for three months to see if any reduction in cholesterol levels might be obtained. There was no lowering of cholesterol levels, and the medication was discontinued when the

patient complained bitterly of insomnia, nervousness, tremor and sweating. The basal metabolic rate at termination of this treatment was plus 31 per cent.

There was no acute illness except for a few days of a pleuritic type of pain for which no etiology was proved, and which was controlled by codeine and salicylates. She died in June, 1947, with a terminal picture of coma.

Necropsy was performed by the Department of Pathology at this hospital. The gross report (with minor incidental findings deleted) was as follows: Xanthomatous biliary cirrhosis with obstructive icterus. Hepatosplenomegaly. Xanthomatosis involving the liver, epicardium, endocardium, pleura, bronchi, trachea, spleen and accessory spleen, bone marrow and skin. Chronic ascending cholangitis. Hemorrhagic diathesis. Recent hemorrhage into the lower gastrointestinal tract and into the subserosa of the colon. Multiple hemorrhages in the omentum, submucosa and mucosa of the small intestine, duodenum, stomach and mesentery. Bile nephrosis. Chronic fibrous pleuritis. Atherosclerosis of the coronary arteries and the aorta. Hematopoiesis in the liver.

Addison and Gull² are given credit for first describing (in 1851) a patient combining skin xanthoma, jaundice and a peculiar form of cirrhosis. Fagge³ and Pye-Smith⁴ individually reported similar cases in 1873, which were fol-

TABLE I
Biochemical Values*

Date	Cholesterol	Total Lipids
4/4/44	2200 mg. %	3.25
6/22/44	1850 mg. %	
7/10/44	1300 mg. %	3.40
10/13/44	996 mg. %	3.18
10/26/44	1107 mg. %	
1/24/45	1955 mg. %	
2/8/45	1430 mg. %	
4/6/45	846 mg. %	3.06
6/26/46	729 mg. %	
2/3/47	425 mg. %	3.35

* All chemical determinations were made by Dr. Henry C. Eckstein, Department of Biological Chemistry, University of Michigan.

lowed by scattered reports of other cases, but there was no correlation of the findings and little agreement as to the etiology. When Thannhauser and Magendanz¹⁰ grouped these findings into a single clinical syndrome, their descriptive requirements included (1) skin xanthoma of "plain and tuberous" variety; (2) enlarged liver and spleen; (3) obstructive type jaundice of years' duration; (4) extremely high values for total cholesterol as well as lecithin, and (5) blood serum which was transparent and not creamy, despite increase in cholesterol and lecithin and low normal values for neutral fat.

The clinical picture of patients with xanthomatous biliary cirrhosis is typical but not specific. The onset is insidious, with itching and jaundice of the obstructive type. The jaundice is persistent but the patient may feel quite well. The skin lesions may be observed with the onset of jaundice, but usually appear later, with a predilection for the hands, feet and elbows and, later, appearance on the eyelids, arms, fingers and buttocks. Liver and spleen are enlarged, smooth and firm, and without nodules or tenderness. Usually there is no ascites. Patients may show bleeding tendencies not readily corrected by vitamin K, and

many die from bleeding varices. There is a very strong sex predilection in that all cases reported are females, except a very few, and these few are warmly disputed by most authorities. The age range is between 30 and 50 except for one instance in a seven year old girl, reported by Herbert.⁶

The differential diagnosis between xanthomatous biliary cirrhosis and other conditions where skin xanthoma may appear is not difficult when one keeps the former condition in mind. Skin xanthomas rarely appear in the usual form of biliary cirrhosis, and in this condition there is no rise in cholesterol or lecithin. The skin lesions, when they do appear, are transient, clearing with surgical resto-

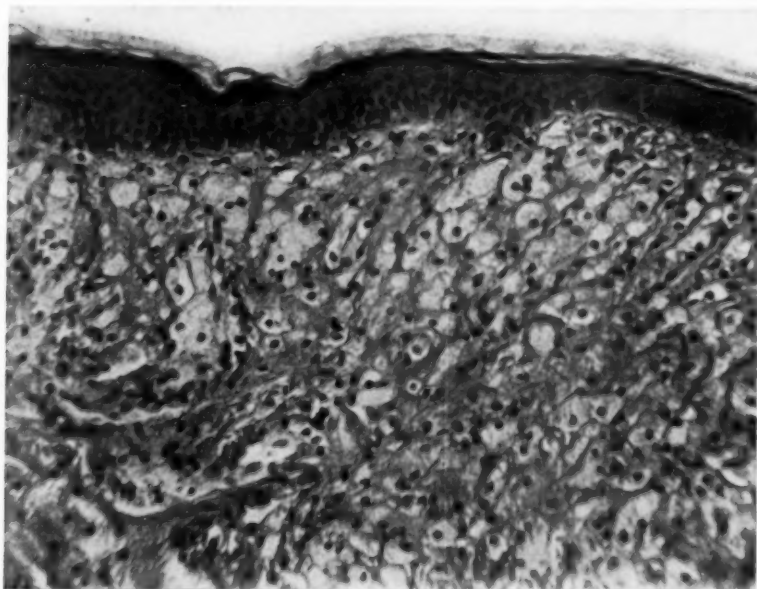


FIG. 3. Skin. The epidermis overlies a mass of lipid-containing foam cells which replace the upper portion of the corium. Cutaneous xanthomatosis, typical of all of the lesions of the skin and of subserous and submucosal plaques as well. Hemalum and eosin stain.

ration of the bile flow or with termination of the disease. The cutaneous lesions in xanthomatous biliary cirrhosis appear early and persist. To distinguish between this condition and such states as hemochromatosis, diabetes, glycogen storage disease, idiopathic hereditary hyperlipemia and transport (secondary) lipemia is not difficult when the laboratory findings and history are considered. It should be stated that as a rule liver function studies are of no real value in differential.

It is admitted by all that the etiology is not clearly understood. It is agreed that xanthoma of the large bile ducts is not the primary insult which starts this disease process. Thannhauser¹¹ originally favored this view but recently has

rejected this, and he and MacMahon⁷ suggest "pericholangiolitic biliary cirrhosis or pericholangiolitic xanthomatous cirrhosis" as a more nearly correct term. The most generally accepted theory now is that xanthomatous biliary cirrhosis must be considered as a primary liver disorder, with secondary development of skin xanthoma and atheroma formation in the inner lining of the arteries and possibly, in rare cases, in the bile ducts. Shay and Harris⁸ recently published a comprehensive review of this subject and reported one case



FIG. 4. Epicardium. A plaque of lipid-containing foam cells is shown beneath the epicardial serosa. No significant inflammatory reaction is present. Hemalum and eosin stain.

with xanthoma of the bile ducts. They state that their case is the second report since 1905 of such findings.

Ahrens¹ and his group believe that this condition may be divided into two classes: (1) the "primary biliary cirrhosis," which corresponds to the earlier term of "pericholangiolitic biliary cirrhosis" of MacMahon and Thannhauser, and (2) a "secondary biliary cirrhosis," resulting from long-standing extrahepatic biliary tract obstruction which is known to cause the same picture with skin lesions and liver changes. Shay and Harris suggest still another term, "hepat-

cellular hypercholesterolemic cirrhosis," caused by hepatotoxic agents, either unknown, as is usual, or recognizable, such as arsenic, viruses or cinchophen.

MacMahon believes that the liver changes are a part of the disease and not the cause of the disease. Autopsies on four of his patients showed a confusing picture, with a large firm liver, extensive fibrosis, fragmentation of some lobules and total loss of others. There were also nodules of regenerated liver tissue, bile stasis, intralobular lipid deposition and still active chronic inflammatory disease. Four points emphasized were: (1) blocking of the finest bile ducts with intralobar bile stasis; (2) nonspecific, chronic inflammatory reaction centered about the smallest bile ducts and junctional ducts in the portal areas; (3) no involvement of the larger bile ducts, and (4) absence of foam cells in liver tissue.

The exact cause of the cutaneous or systemic xanthomatous lesions is not known. It may be increased mobilization, as in diabetes or renal disease; diminished excretion, as with obstruction of extrahepatic biliary ducts; or overproduction, as in endogenous metabolism. Most writers feel that no correlation exists between severity of disease and the number or extent of skin lesions.

Treatment of this disease state is palliative and consists of a low animal cholesterol diet, amino acids, transfusions and treatment of pruritus. Vitamin K may be given to combat hypoprothrombinemia. In retrospect, however, the above treatment, including T-tube drainage, did not seem to alter our patient's clinical course.

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**APPEARANCE OF MILIARY TUBERCULOSIS FOLLOWING
THERAPY WITH ACTH AND CORTISONE IN
A CASE OF ACUTE DISSEMINATED
LUPUS ERYTHEMATOSUS***

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ALTHOUGH a great deal of experimental work has been done on animals demonstrating the enhancing effect of ACTH and/or cortisone upon the evolution and development of tuberculous lesions,¹⁻¹¹ there are relatively few case reports in the literature dealing with this phenomenon in humans.¹²⁻¹⁹

Presented in this report is a case of miliary tuberculosis, authenticated by postmortem examination, which developed during the course of extensive ACTH and cortisone therapy for acute disseminated lupus erythematosus.

CASE REPORT

A 49 year old single white female was admitted to the Jewish Hospital of Brooklyn for the first time on October 20, 1951, for joint pains, anorexia, fever, malaise and weight loss.

Two months prior to admission the patient had noted the onset of nonmigratory rheumatic pains in the knees and elbows unassociated with inflammatory changes. These lasted for one month and then disappeared. Following this, anorexia and marked weakness appeared which persisted to admission. There was a 12 pound weight loss, accompanied by a distinct aversion to meat, but no other pertinent gastrointestinal or systemic symptomatology. There had been two questionable episodes of acute rheumatic fever in the past, but no heart murmurs were reported. The patient's father had died of lupus vulgaris.

Physical examination revealed a chronically ill, cachectic female. Her temperature was 102° F.; pulse, 92; respirations, 22; blood pressure, 96/54 mm. of Hg. There was an area of erythema with dilated venules over the left malar eminence. Healing ulcerations were noted over the hard and soft palates, and the lips were dry and cracked. A small, semi-hard, discrete, left supraclavicular node was noted. Heart and lungs were normal, but abdominal examination revealed a smooth liver edge two fingerbreadths below the costal margin, and a questionably enlarged spleen. A scaly rash on an erythematous base was present on the anterior surface of the knees, the superior sacral area and over the posterior lumbodorsal area.

While in the hospital the patient ran a remittent temperature ranging as high as 104° F. Bibasilar râles developed in the posterior chest, but chest films were consistently negative (figure 1). Persistent tachycardia was present. Penicillin and streptomycin therapy produced no response. The patient's hemograms revealed a normochromic, normocytic anemia with an essentially normal white count and differential. Diagnostic lumbar puncture was nonrevealing. On November 2 a localized erythematous patch appeared over the right malar eminence. There was no history of exposure to tuberculosis, and studies for tuberculous infection (viz., chest x-rays, sputum studies, gastric washings and urine cultures) were negative. The urine showed a persistent pyocyanus infection that was treated with terramycin. Sternal marrow puncture on November 7 revealed numerous LE (Hargraves) cells

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in the preparation. All other laboratory investigations, including complete gastrointestinal x-rays, were noncontributory. On the basis of the finding of LE cells and of the clinical picture, a diagnosis of acute disseminated lupus erythematosus was made. Intravenous ACTH, 20 mg. daily, was initiated on November 7. By November 9 the temperature had fallen to 100° F. On November 10 oral cortisone, in a

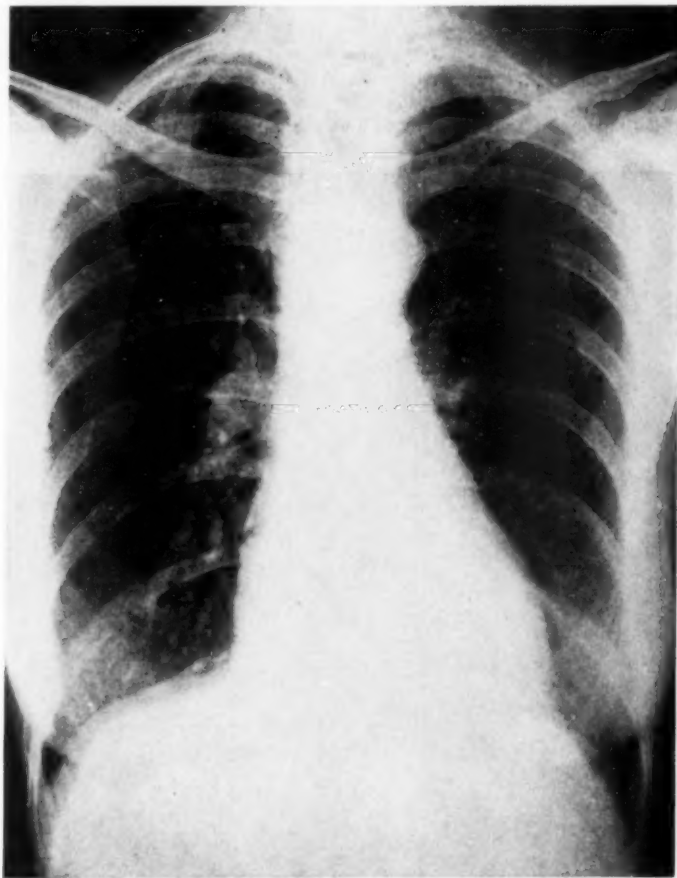


FIG. 1. Chest plate taken on the first admission (10/23/51), showing no evidence of tuberculosis or any other disease.

dosage of 50 mg. daily, was added; it was continued until discharge and then at home. On November 16 ACTH was stopped. The patient had a complete remission while receiving hormonal therapy and was discharged, markedly improved, on November 22, 1951.

She was readmitted to the hospital on March 18, 1952, for marked weakness, anorexia, weight loss, pyrexia and a nonproductive cough.

During the interval between admissions she had been maintained on oral cortisone, ranging in dosage between 50 and 150 mg. per day.

The patient was moderately well for about one month when, due to progressive weakness, she became bed-ridden. Three weeks before re-admission she had developed a persistent, nonproductive cough, with daily elevations of temperature to 104° to 105° F. One week before re-admission, transient periods of mental confusion appeared. There were no joint symptoms and no symptoms referable to the gastrointestinal or genitourinary systems.

During the last week at home cortisone was discontinued. Massive doses of penicillin were given intramuscularly, with no effect.

Physical examination on this admission revealed a cachectic white female who appeared both acutely and chronically ill and exhibited periods of disorientation. Her

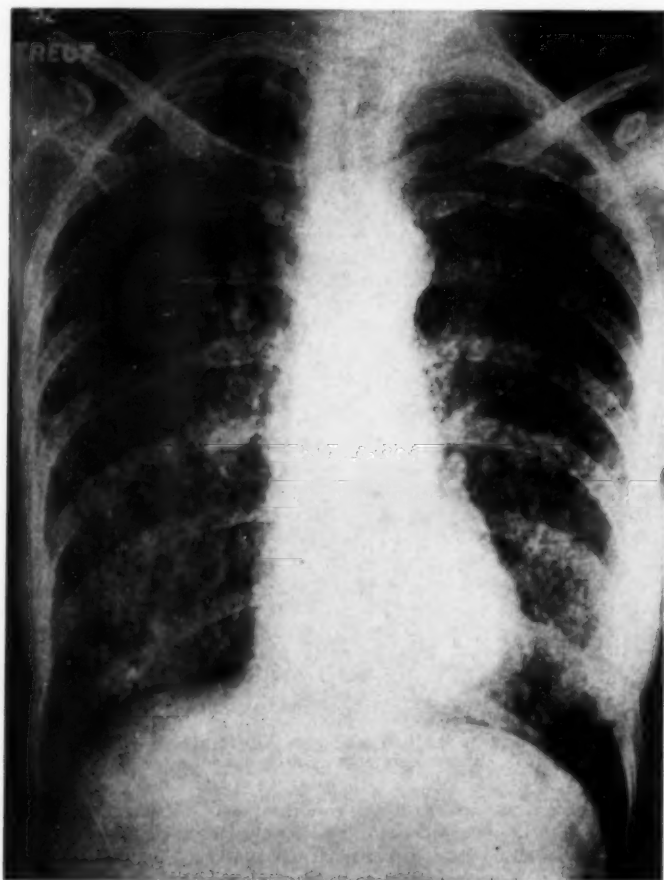


FIG. 2. Chest plate taken on the second admission (3/31/52), showing miliary infiltration of both lung fields. Earlier films taken on this admission were essentially the same.

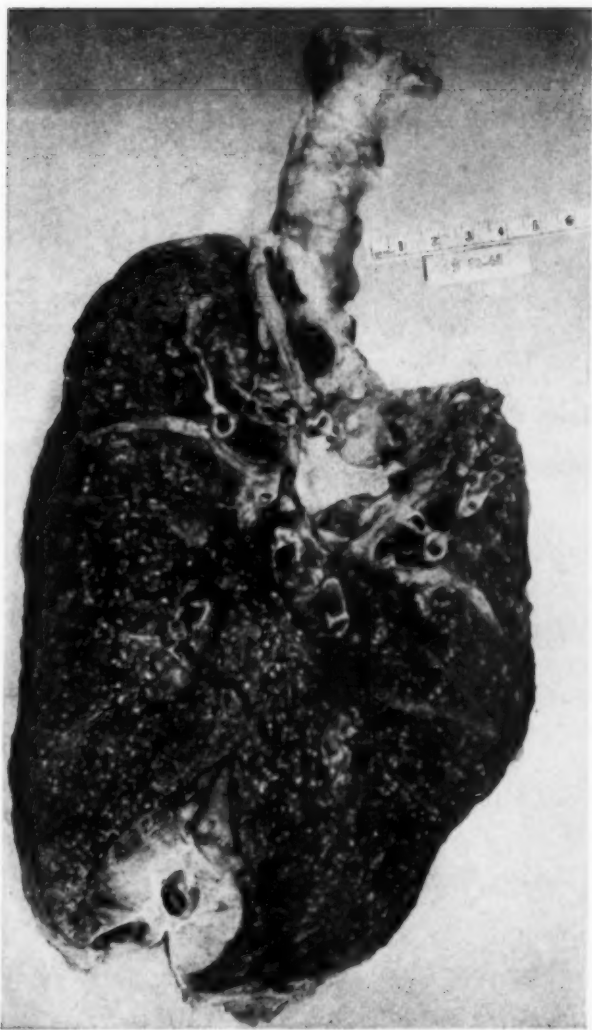


FIG. 3. The gross cut surface of the lung, showing numerous grayish-white nodular deposits in all lobes.

skin was dry and scaly, with poor elasticity. Bilateral malar erythema was present, a fixed stare expression was noted, and extraocular movements were sluggish. Mucous membranes were pale and the tongue was moderately dry and coated. Examination of the lungs revealed coarse subcrepitant râles throughout both lungs, with a pleural friction rub heard on the left side anteriorly. Increased percussion resonance and intensity of the breath sounds were noted at this site. Examination of the heart

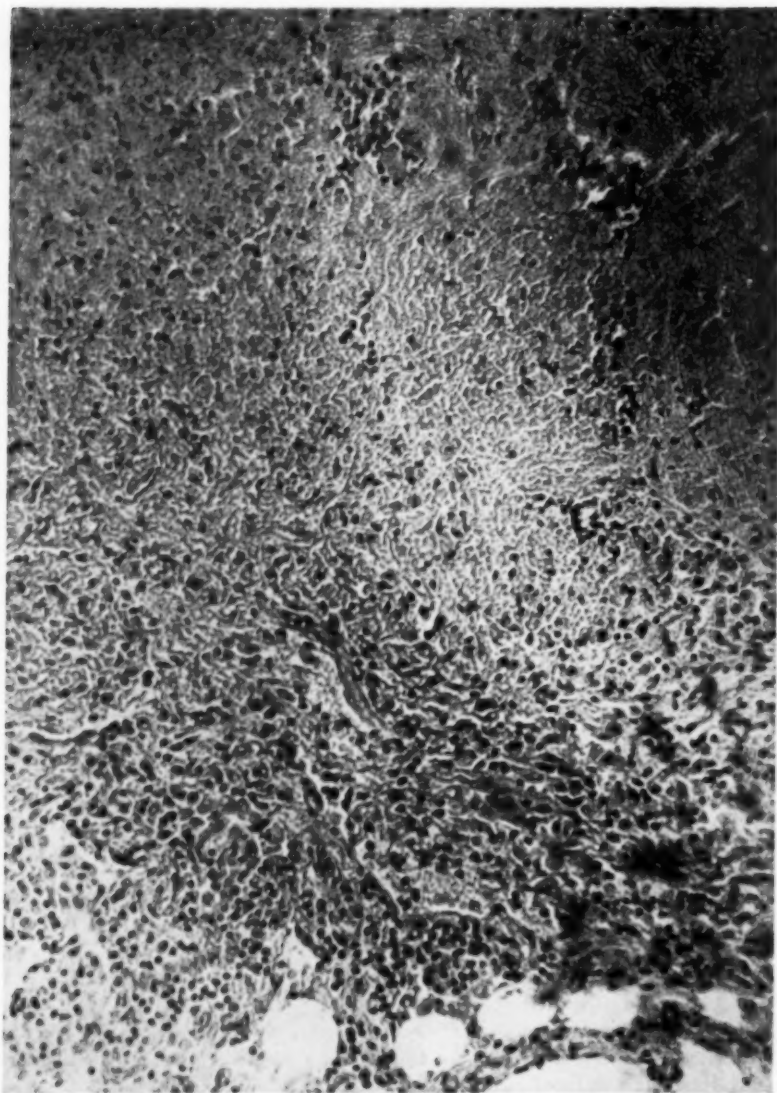


FIG. 4. Microscopic section of lung. For description see text.

revealed a sinus tachycardia, an apical systolic murmur with a snapping M_1 , an early apical diastolic blow, and a P_2 moderately snapping in character. The remainder of the physical examination, including neurologic, was negative.

A chest film taken on March 18 showed a miliary infiltration of both lung fields

which was considered to be tuberculous in origin (figure 2). The blood count revealed a hemoglobin of 59 per cent, with 3.41 million red blood cells; white blood cells, 8,800, with 74 polymorphs, 17 lymphocytes and 9 bands in the differential count. Platelets were adequate, and toxic granulation of some of the polymorphs was noted.

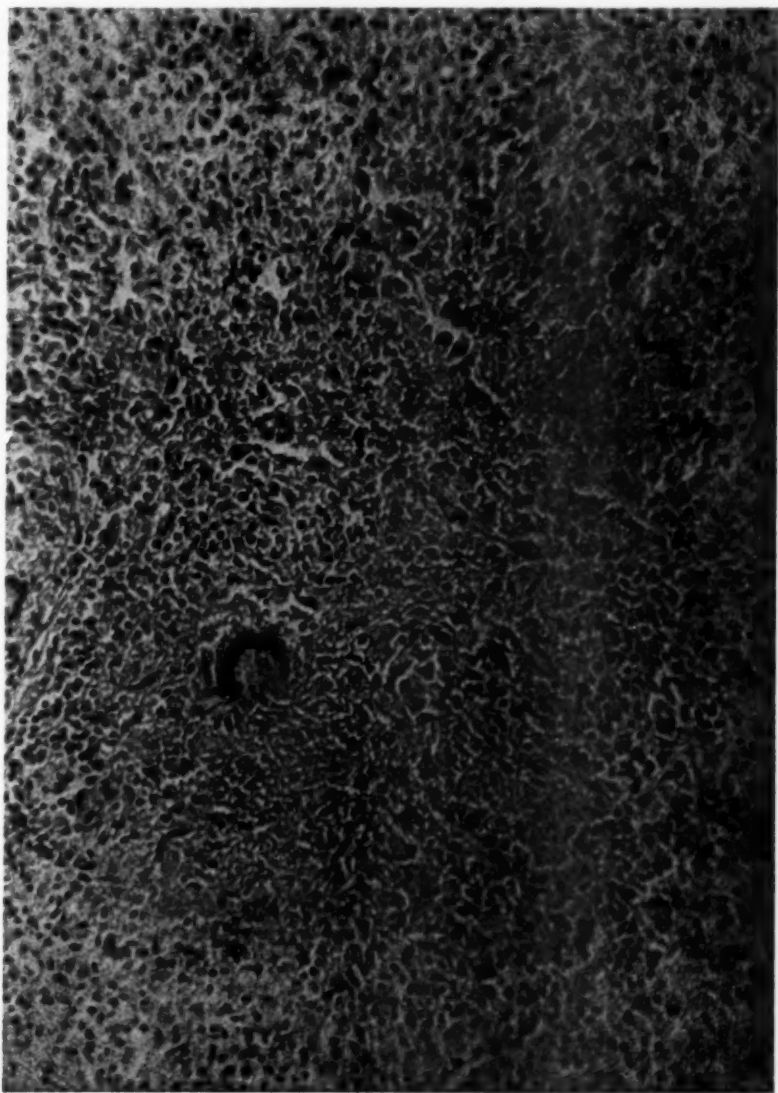


FIG. 5. Microscopic section of spleen showing Langhans' cell.

The bone marrow revealed toxic degeneration of white cell elements, with extracellular globular bodies but no characteristic LE (Hargraves) cells. Blood chemical studies showed normal liver function and electrolyte values.

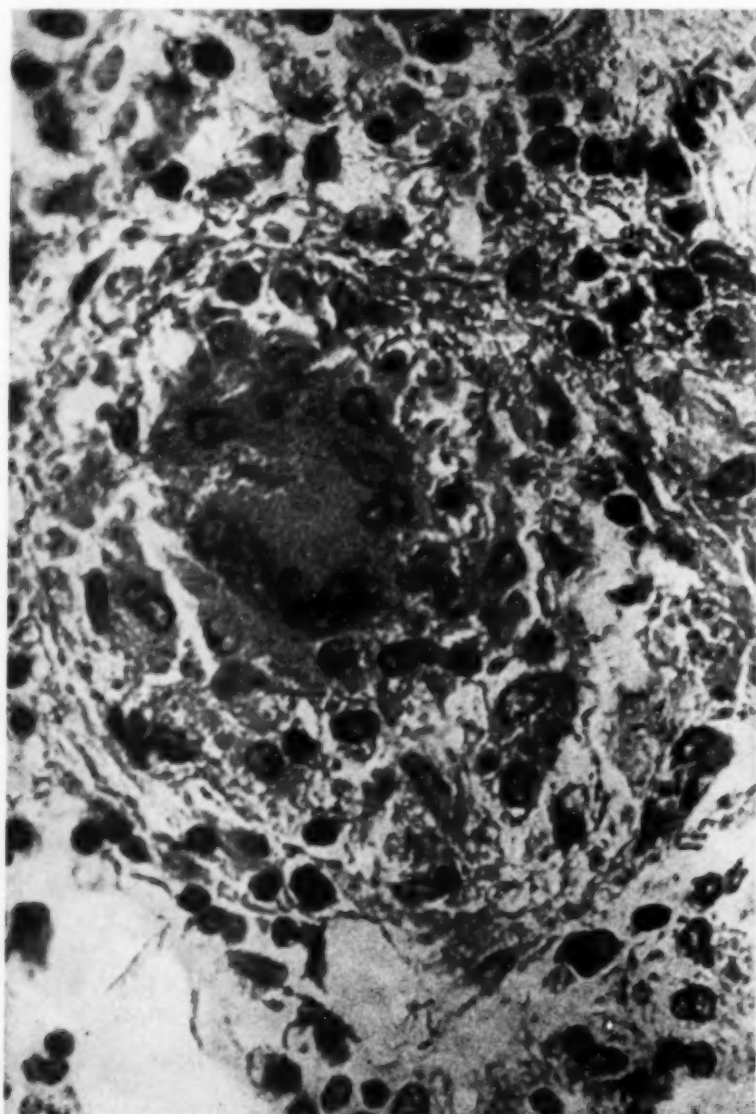


FIG. 6. Microscopic section of bone marrow showing Langhans' cell.

Because it was felt that there was a very strong possibility of disseminated miliary tuberculosis in this patient, steroid therapy was withheld and procaine penicillin, 600,000 units intramuscularly daily with 2 gm. of streptomycin daily, was started on March 20. This was supplemented with 12 gm. of para-aminosalicylic acid daily. Lumbar puncture was negative in all respects, including culture for acid-fast bacilli. Two lung biopsies with the Silverman needle, four days and 10 days after admission, revealed only nonspecific inflammation with necrosis and fibrosis. All attempts to isolate acid-fast bacilli were negative except for culture of the aspirate from the last lung biopsy, which revealed tubercle bacilli four days after the specimen was obtained. Shortly after institution of antibiotic and chemotherapy, the patient became afebrile and more lucid, and was generally much improved. Thirteen days after admission, however, she suddenly developed marked respiratory distress and cardiovascular collapse, became comatose and died.

Postmortem examination revealed the following: All elements of the heart were normal. There was some difficulty in stripping off the kidney capsule, but on microscopic examination the kidney was found to be normal, with no pathologic changes consistent with lupus erythematosus. The endocrine glands showed no abnormality other than some mild pituitary hyperplasia.

Upon gross examination the lungs showed thickening of the pleura, with diffuse grayish white nodules on section (figure 3). There was enlargement of the tracheobronchial lymph nodes. Microscopically, the lung showed several irregular tubercles with a necrotic central area. The alveoli were filled with a pink staining granular and hyaline material admixed with numerous degenerating leukocytes. There was a poor attempt by the fibroblasts to localize the necrosis, and the inflammatory reaction was minimal. Giant cells were absent. The bronchioles showed desquamation of epithelium; the adventitia was infiltrated with round cells. Diffuse caseous necrosis was present in the tracheobronchial nodes, with obliteration of cellular detail. A few Langhans' giant cells were present, and numerous epithelioid cells were noted (figure 4).

The liver and spleen were grossly normal, but on microscopic examination showed irregularly scattered tubercles, with Langhans' giant cells surrounded with fibrous tissue and epithelioid cells. The centers were necrotic and acellular (figure 5). Scattered tubercles were also found in the bone marrow (figure 6).

DISCUSSION

Considerable research has been reported dealing with the effect of cortisone and ACTH upon experimentally induced tuberculosis in animals.¹⁻¹¹ These animals include rabbits,^{1, 6} rats,^{2, 3, 4, 5, 8} guinea pigs^{7, 9, 11} and mice.¹⁰ The majority of the investigators have found these hormones to have a deleterious effect upon animals with tuberculosis, namely: (a) Diminution in granulation tissue formation. (b) Increased dissemination of the tuberculous lesions. (c) Increased necrosis and caseation. As a result, these animals showed an increased and earlier mortality when compared with control animals untreated with these hormones.

Rats, normally resistant to tuberculosis, developed diffuse lesions when infected with tubercle bacilli in the presence of cortisone administration.^{2, 3, 4, 5, 8} As mentioned above, when these animals were sacrificed they showed diffuse necrotic lesions with overwhelming numbers of tubercle bacilli. In cases where streptomycin and cortisone were employed together,^{3, 8} the streptomycin proved less effective than when used alone. Similar results were obtained with guinea pigs^{7, 9, 11} and mice.¹⁰

Experimental studies were done on rabbits¹ whereby the animals were sensitized to and then tested with tuberculin. Those given ACTH exhibited 60 to 90 per cent less reaction than control rabbits. In another study,⁶ cortisone-treated rabbits and controls were exposed to tuberculosis via inhalation. In the cortisone-treated rabbits, a greater number of tubercles were noted in the lungs, with greater caseation than in the controls. Instead of disseminating widely, however, the lesions were fairly well localized to the regional hilar nodes, despite a marked increase in the number of multiplying bacilli in the primary lung site. Thus, the cortisone-treated rabbits acted somewhat like those with native resistance. These studies are in direct contrast with the findings in other animals.

The enhancing effect of cortisone and ACTH upon the dissemination of tuberculosis has been fairly well documented in experimental animals. With this in mind, clinicians have been wary of the use of these hormones in humans with evidence of tuberculosis. Reports are few of cases developing evidence of tuberculosis following therapy with these hormones where tuberculosis preceding therapy was not clinically apparent.

Five such cases with rheumatoid arthritis treated with cortisone alone, or with ACTH and then cortisone, are reported.^{12, 13, 14, 15} None of these cases had evidence of clinical tuberculosis prior to institution of hormone therapy, but all five developed such evidence, one terminating fatally. Two similar cases with polyarteritis nodosa are reported,^{15, 6, 16} one treated with ACTH, the other with cortisone. The latter¹⁶ developed fatal miliary tuberculosis. In neither of these cases was there clinical evidence of tuberculosis prior to hormonal therapy.

Thirteen cases are reported^{16, 17, 18} where ACTH alone or ACTH and cortisone were administered to cases with known pulmonary tuberculosis. In all of these cases an improvement in systemic symptoms associated with some euphoria and improvement in appetite was noted. In 11 of these cases^{16, 17} a reversal in tuberculin positivity was noted. In nine cases^{17, 19} no change in the pulmonary lesions or worsening of these lesions was noted. In four of these cases,¹⁶ where laryngeal tuberculosis was present, a decrease in the size of these lesions occurred. When ACTH was withdrawn no change in the lesions occurred but there was an exacerbation in the systemic symptoms. One may postulate a masking effect on the part of these hormones, whereby they improve the sense of well-being of the patient without actually improving the tuberculous process, and probably even aiding in its spread.

From the case presented above, it seems rational to assume that ACTH and cortisone therapy can exacerbate old tuberculous lesions and facilitate widespread dissemination of the tubercle bacilli. Within a space of four months while receiving hormone therapy, our patient, apparently free from tuberculosis on thorough investigation, developed a widespread, fulminating, widely disseminated miliary infection, with involvement of lung, liver, spleen, lymph nodes and bone marrow. Comparison of the two chest films (figures 1 and 2) demonstrates the rapid dissemination of the infection.

The microscopic examination of the organs in this patient bears out the thesis that impaired granulation and fibrotic tissue formation in patients receiving ACTH or cortisone may be responsible for the harmful effects of their

administration. In the lungs the prominence of necrosis and caseation in the tubercles is marked, as is the absence of fibroblastic inflammatory reaction around these lesions.

Unlike some of the cases reported above,^{16, 17, 18} there was no masking of systemic symptoms by cortisone, as fever and cough were prominent and the patient's general debility was marked.

It is interesting to speculate on the specificity of the Hargraves LE cell phenomenon²⁰ in view of the absence of pathologic confirmation of acute disseminated lupus erythematosus on post mortem. This conjecture is not within the scope of this report. Suffice it to say that, in addition to the positive LE preparation, the clinical criteria for this diagnosis on the first admission seem to have been adequate.

SUMMARY AND CONCLUSION

1. A case report is presented in which a patient receiving ACTH and cortisone for acute disseminated lupus erythematosus developed a fatal miliary tuberculosis.

2. A review of the literature dealing with experimental animals indicates the tendency of ACTH and cortisone to diminish resistance to tuberculous infection in rats, mice and guinea pigs, though not in rabbits.

3. Cases are cited from the literature demonstrating the appearance of tuberculous infection in previously unaffected individuals during ACTH and cortisone therapy, although known cases of tuberculosis manifested systemic amelioration while undergoing therapy.

4. This case adds support to the observation that ACTH and cortisone may accelerate dissemination of a preëxisting tuberculous focus, whether apparent or unsuspected.

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ACUTE PORPHYRIA: A CASE REPORT *

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ACUTE porphyria is an inborn or acquired error of metabolism characterized by the urinary excretion of abnormal quantities of uroporphyrin, coproporphyrin and porphobilinogen, and manifested clinically by intermittent attacks of acute abdominal pain, constipation, neurologic symptoms or psychic disturbances. The varied clinical features, as well as the pathologic chemistry of the condition, have been adequately reviewed,^{1, 2, 3, 4, 5} and the present authors can add nothing to these excellent presentations. One point deserves emphasis, however. Acute porphyria may present such varied symptoms that the diagnosis is often not considered for several years after the onset.⁶ The test for urinary porphobilinogen described by Watson and Schwartz⁷ is a simple laboratory procedure but is highly specific,⁸ the test being positive only in acute porphyria and in some instances of chronic porphyria.⁹ The diagnosis of acute porphyria should be considered and the urine tested for porphobilinogen in every case of unexplained abdominal pain, bizarre neurologic disturbances and severe psychoneuroses.

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The treatment of acute porphyria remains unsatisfactory. Watson and Larson¹ recommend avoidance of such drugs as Sulfonal (sulfonmethane), Trional (sulfonethylmethane) and barbiturates, and symptomatic treatment with Demerol (meperidine hydrochloride), Methodon, warm baths and warm saline enemas.

Liver extract and vitamins of the B group, especially riboflavin, folic acid and vitamin B₁₂, have been widely recommended,¹ but the results seem either questionable^{10, 11, 12, 13} or completely negative.^{14, 15, 16} Watson states¹ that liver extract and the B vitamins have been disappointing in his hands.

Atropine^{16, 17, 18} and belladonna¹⁸ have been of no value. Tetraethylammonium chloride, Priscoline (2-benzyl-imidazoline hydrochloride), tubocurarine and splanchnic block were of temporary or partial benefit in one patient, while Benodaine (pipcroxan hydrochloride) had no effect.¹⁶ Neostigmine has been reported to relieve the pain temporarily,¹⁷ but other authors report it to have no effect.^{14, 19, 20} Urecoline (bethanechol chloride) relieved obstipation but not the pain in one instance.¹⁸

Intravenous calcium gluconate has been thought by some authors^{10, 11} to help abort an exacerbation of acute porphyria, while others have found it to have no effect.^{14, 16, 21} Kaolin has been used in one case²² to adsorb porphyrins within the gastrointestinal tract. Some clinical improvement and a slight fall in urinary porphyrin excretion seemed to occur, but the effect was not definite. Cobra venom afforded temporary benefit in one case.²³ Electric shock therapy has been recommended for the treatment of psychiatric symptoms.^{24, 25}

The possibility of adrenal dysfunction in acute porphyria has been considered,^{26, 27} but apparently only a compensatory adrenal hyperfunction is involved.²⁷ In reported cases neither ACTH^{24, 28} nor cortisone^{20, 29} affected the clinical course of acute porphyria; however, Watson³⁰ reports knowledge of several cases which seem to have derived benefit from ACTH.

Intravenous procaine hydrochloride is reported to have produced several dramatic remissions in one patient.²⁸

CASE REPORT

A 20 year old white housewife was admitted to the hospital on January 6, 1952, giving a history of having had intermittent severe cramping abdominal pain and obstipation for two weeks. This pain had been maximal in the right lower quadrant, though present throughout the abdomen. Frequent narcotics had been required for pain. The urine had been dark red, and acute porphyria had been diagnosed by the referring physician.* The past medical history was not relevant, and in particular revealed no previous similar attacks. There was no known precipitating toxic agent. The family history was noncontributory except that the paternal grandmother had died at the age of 37 following an illness of one year's duration which could have been acute porphyria, though no such diagnosis was considered at the time. A single urine sample was obtained of all living near relatives (father, mother, sister, brother, paternal uncle), and gave a negative test for porphobilinogen.

Physical examination revealed an acutely ill white female having severe generalized abdominal cramping and tenderness, maximal in the right lower quadrant. No definite neurologic defects were noted, and physical examination was otherwise within normal limits.

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The hemoglobin, hematocrit, differential leukocyte count, sedimentation rate and red blood cell fragility were normal throughout hospitalization. The total leukocyte count was normal with the exception of an isolated count of 13,700 per cubic millimeter on the fifth hospital day. The fasting eosinophil count was normal on admission. The urine color varied from a light red to nearly black and gave a strongly positive test for porphobilinogen, confirming the diagnosis of acute porphyria, presumably idiopathic. Since the urine contained gross pus and gram negative bacilli, the patient was given dihydrostreptomycin and later chloromycetin (table 2). Table 1 shows the urinary porphyrin excretion on admission. The urinary porphobilinogen was negative in Dr. Watson's laboratory, but this was undoubtedly caused by improper preservation of the urine by us, since the hospital laboratory found a positive test for porphobilinogen in the initial urine specimen submitted to them.

Blood chemical studies including sodium, chloride, carbon dioxide combining power, calcium, phosphorus, non-protein nitrogen and bilirubin all remained within normal limits throughout hospitalization, with the exception of one sodium determination of 131 mEq./L. The serum concentration of potassium remained slightly low, 3.8 to 4.0 mEq./L. (normal in this laboratory, 4.5 to 5.6), and the patient was given enteric coated potassium chloride, 0.3 gm. three times daily. The total serum proteins

TABLE I
Urinary Porphyrin Excretion*

Date	Coproporphyrin Gamma per day	Uroporphyrin Gamma per day	Porphobilinogen
1-7-52 (Prior to ACTH Therapy)	572	60,939	Negative**
1-10-52 (After ACTH Therapy)	840	71,040	3+
1-13-52 (After Procaine Hydrochloride Therapy)	690	44,160	2+
6-4-52 (During Remission)	986	31,190	Negative

* Generously determined by Dr. Cecil J. Watson, Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

** Urine not properly preserved.

rose from 5.3 to 6.5 gm. per cent during hospitalization, while the serum globulin rose from 2.2 to 3.4 gm. per cent, the albumin remaining approximately the same. Liver impairment on admission was indicated by a bromsulfalein dye retention of 17 per cent in 45 minutes, and a thymol turbidity of 5 units (normal, 4 units or less). Tests toward the end of hospitalization were 7 per cent retention and 4 units, respectively. Roentgenographic examinations of the chest and colon were normal.

Further hospital course and treatment can best be followed by reference to table 2. During the first 40 hours the patient was given only supportive therapy and narcotics for pain. Because of the large amount of narcotics required for a tolerable level of pain relief, drugs were changed frequently. After a pretreatment 24 hour urine sample had been collected, the patient was started on a slow intravenous drip (15 to 25 drops per minute) of ACTH, receiving 10 mg. in 500 c.c. 0.2 per cent KCl in 5 per cent dextrose on the first day and then 25 mg. daily on two subsequent days (January 9 and 10). On this treatment the fasting eosinophil count fell from a pretreatment level of 211 cells per cubic millimeter to 16 and then to 0 cells per cubic millimeter, indicating satisfactory adrenal stimulation. The patient had not improved; she was still requiring large amounts of narcotics, and the urinary porphyrin excretion had not been significantly altered (table 1).

One hundred milligrams of Octin (6-methylamino-2-methylheptene) intramuscularly were found to give from three-quarters of an hour to four hours' relief of pain,

depending on the severity of pain at the time of the injection; and 10 c.c of a 10 per cent solution of calcium gluconate given intravenously were found to produce from one and one-half to two hours' freedom from pain. Comparable placebo injections had no significant effect. These medications were given freely to reduce the use of narcotics. No significant alleviation of pain was produced by 400 mg. of tetraethylammonium chloride given intravenously over a 20 minute period.

Because of the encouraging report of Grubbschmidt²³ in producing a remission with intravenous procaine hydrochloride, it was next decided to use this agent. Five hundred cubic centimeters of 0.2 per cent procaine hydrochloride in 0.45 saline solution were given slowly intravenously (15 to 25 drops per minute) daily for two days (January 11 and 12). Following the second infusion there occurred a dramatic reduction in the use of narcotic and other pain-relieving medications (table 2), with a

TABLE II
Summary of Treatment

Therapy per 24 hours	Date, January, 1952																				
	7	8	9	10	11	12	13	14	15	16	17	18*	19	20	21						
Demerol, mg. (I.M.)	825 825	1,000					175	400				100									
Pantopon, mg. (S.C.)		20	90																		
Dilaudid, mg. (S.C.)			8	16					4			4			2						
Dolophine, mg. (S.C.)				10	40	40															
Morphine, mg. (S.C.)							30														
Octin, mg. (I.M.)			200	100	400	400		100	200	200	200		200	200	200						
Calcium gluconate, gm. (I.V.)			1.0	1.0			1.0		1.0	1.0			1.0	2.0							
ACTH, mg. (I.V. slowly)		10	25	25																	
Procaine HCl, gm. (I.V.)					1.0	1.0		1.0							1.0						
Intravenous fluids, c.c.	1,000	2,000	2,000	2,000	500	500		500							500						
Potassium chloride, gm. (P.O.)			0.7	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.7						
Dihydrostreptomycin, gm. (I.M.)					1.0	1.0	1.0	1.0	1.0	0.25											
Chloromycetin, gm. (P.O.)										0.5	0.75	0.75	0.75	0.75	0.75						

* Moderate recurrence of abdominal pain for one day associated with colon x-ray.

corresponding clinical and subjective improvement in the patient. Urinary porphyrin excretion (table 1) was reduced, but not significantly so. To achieve further improvement, a third infusion of procaine was given on January 14, and following this there was a further reduction in narcotic medication, with continuing clinical improvement. Little narcotic medication was required subsequently, the patient being controlled by occasional Octin or calcium gluconate. On January 18, three injections of narcotic were required; this was due to a temporary exacerbation of symptoms, occasioned by the roentgenographic examination of the colon. Mild pain continued to the time of discharge, however, and a fourth infusion of procaine was given on January 21. The patient was instructed to take two therapeutic vitamin capsules (Squibb's Theragran) daily at home, and Dormison (methylparafynol), 250 mg. nightly as necessary for sleep.

Subsequent history obtained from the referring physician revealed that the patient continued to do well at home for about five weeks, after which she had another, milder exacerbation, controlled by Priscoline. The patient was last seen on June 4, 1952, at which time she was continuing in remission, but was estimated to be four months' pregnant. It has been reported that pregnancy may produce an improvement in symptoms of acute porphyria,³¹ but the recorded protocol is not convincing on this point, and other authors report no significant change,³² or even an increase in pain and vomiting.³³

DISCUSSION

Evaluation of the efficacy of any treatment of acute porphyria is made difficult by its natural tendency for exacerbation and remission, as well as by the relative rarity of the disease, which makes it impossible for one individual to examine a significant number of patients in a short time. Despite this fact, we feel that certain statements are justified. ACTH did not alter porphyrin excretion or symptoms, confirming previous reports.^{24, 28} Intravenous procaine hydrochloride, on the other hand, while not altering porphyrin excretion significantly, may have produced symptomatic remission. Other possible explanations of the remission include the natural course of the disease, as well as the Octin and calcium gluconate given at the same time. We think, nevertheless, that this patient confirms the results of Grubbschmidt²³ and that this agent deserves further trial, especially in such severely ill patients as the one reported here, who required large amounts of narcotics for a tolerable relief of pain. Both Octin and calcium gluconate repeatedly produced temporary relief of pain, whereas comparable placebo injections gave no significant relief. Here again, we feel that these two agents should be tried for symptomatic relief. Tetraethylammonium chloride, on the other hand, gave no significant relief; however, this was given during a severe attack of pain, and in the previously reported use of this drug,¹⁸ it likewise failed in one instance when severe pain was present. No conclusion appears justified as to the effect of pregnancy on acute porphyria in this patient. The rôle of the urinary tract infection and antibiotic therapy is likewise impossible to assess.

Excretion of uroporphyrin and coproporphyrin remained high during remission with the patient four months' pregnant (table 1), but porphobilinogen was no longer present, a not uncommon finding during remission.⁹

CONCLUSIONS

1. A case of acute idiopathic porphyria has been presented.
2. ACTH appeared to alter neither the course of the disease nor the urinary excretion of porphyrins. The decline in circulating eosinophils following this therapy was evidence of adequate adrenal reserve.
3. Tetraethylammonium chloride did not affect the pain.
4. Both Octin and calcium gluconate appeared to afford temporary relief of pain, as did various narcotic medications.
5. A remission was produced coincidental with the intravenous administration of procaine hydrochloride. Though we have not proved the procaine to be necessarily involved in this remission, we consider it to be deserving of further trial.

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**PULMONARY ARTERIOVENOUS FISTULA ASSOCIATED WITH
HEREDITARY HEMORRHAGIC TELANGIECTASIS: A
REPORT OF THEIR OCCURRENCE IN A
FATHER AND SON ***

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PULMONARY arteriovenous fistula is a relatively rare disorder of the circulation which is familiar to most cardiologists and thoracic surgeons. It should be of interest to all physicians. We wish to reiterate the fundamental relationship between pulmonary arteriovenous fistula and hereditary hemorrhagic telangiectasis, to summarize their important clinical characteristics, and to discuss two cases occurring in a family, one of which was cured by lobectomy.

Hereditary hemorrhagic telangiectasis is a primary vascular disease characterized by cutaneous, mucosal and visceral telangiectasis and angiomata, hemorrhages and a hereditary transmission. The lesions are commonly seen on the face and on the mucosal surfaces of the lips, tongue, mouth and gastrointestinal tract. The severity of the hemorrhages is extremely variable, depending upon the location, fragility and size of the involved vessels. Repeated hemorrhages result in secondary anemia, chronic debility and, if severe, death. The hereditary nature of the disease is unquestionable. The vascular defect is transmitted as a dominant characteristic affecting both sexes. It has been stated that the hereditary factor is constant and, if not demonstrated, the failure is due to atavism.¹ According to Wintrobe² the condition was first described by Sutton in 1864, and the subsequent reports of Rendu, Weber and Osler established it as a clinical entity. With the passing years, more than 1,000 cases of the disease have been reported, and in these cases angiomatous lesions have been found in nearly every conceivable portion of the body.³

The pulmonary lesions have been called angiomata, varices, aneurysms, cavernous hemangiomas and arteriovenous fistulas. In many of the original descriptions of pulmonary arteriovenous fistula, the relationship of this pulmonary lesion to hereditary familial telangiectasis either was ignored as unimportant or

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was unrecognized; but as more cases are recognized and studied, this fundamental relationship is being emphasized.⁴ According to Burchell and Clagett,⁵ the pathologic lesions of pulmonary arteriovenous fistula were first described by Churton in 1897. Forty-two years later, Rodes⁶ and Smith and Horton,⁷ in separate reports, made significant contributions by calling attention to the definite clinical syndrome associated with these pulmonary lesions. All these studies were culminated in 1942 by Hepburn and Dauphinee's⁸ stimulating report of a cure following pneumonectomy. Since 1942, more than 65 cases of pulmonary arteriovenous fistula have been presented in the medical literature.⁹ This tremendous increase in the reported incidence of the condition reflects the interest with which the medical profession has received these definitive studies.

The classic clinical features of pulmonary arteriovenous fistula are largely the result of chronic anoxemia due to the shunting of blood directly from the pulmonary arterial system into the systemic arterial system, bypassing the pulmonary capillary bed. The degree of anoxemia is dependent upon the volume of the shunt, i.e., the volume of blood containing incompletely saturated hemoglobin which it is capable of shunting per unit of time. If the degree of anoxemia is minimal the symptoms are minimal, and if the degree of anoxemia is severe the symptoms are severe.

The common subjective symptoms are dyspnea, dizziness, faintness, palpitation, pain in the chest, thick speech, headache and paresthesias. Characteristic physical findings are cyanosis and clubbing of the fingers and toes. The heart usually is normal on percussion and auscultation, but auscultation over the lung may reveal a bruit which, if present, may or may not have the continuous characteristics of systemic arteriovenous bruits. The intensity of the murmur often increases in inspiration and decreases in expiration. Laboratory investigations usually reveal polycythemia, elevated hematocrit, increased total blood volume and decreased oxygen saturation of the arterial blood.

Roentgenologic examination of the lungs is of great diagnostic importance. There is usually a lobulated opacity with bandlike linear or sinuous trunks connected to the hilus. Fluoroscopy may reveal pulsation both in the lesion and in the hilus on the same side. Valsalva's test (deep inspiration followed by forcible expiration against a closed glottis) may result in a decrease in the size of the shadow, whereas Mueller's test (deep expiration followed by forcible inspiration against a closed glottis) may cause an increase. The importance of the roentgenologic examination lies not only in the diagnosis of the syndrome itself but also in the determination of the number of lesions, for the fistulas are more likely to be multiple than single. If any surgical procedure is planned, the proper assessment of the number and size of various fistulas is of the utmost importance.

The conditions with which pulmonary arteriovenous fistula might be most often confused are congenital heart disease and polycythemia vera. If a patient presents himself for examination with cyanosis, clubbing of the fingers and toes, and polycythemia, congenital heart disease would be the most common etiologic condition, but detailed examination should demonstrate the absence of cardiac disease. The characteristic morphologic changes in the peripheral blood which accompany polycythemia vera, i.e., immature leukocytes, basophilia and an increased platelet count, should serve to prevent its confusion with pulmonary

arteriovenous fistula. In either instance, the presence of the characteristic pulmonary shadow of pulmonary arteriovenous fistula should clarify the diagnosis.

The treatment of a pulmonary arteriovenous fistula is surgical. Local excision, segmental resection, lobectomy or pneumonectomy may be required, depending on the location and size of the lesion. If the lesions are multiple, more than one procedure may be necessary. An ample supply of whole blood should be available before any surgical procedure is attempted, since alarming hemorrhage may occur either from inadvertent injury to the enlarged, friable and often anomalous pulmonary vessels, or from collateral vascular channels present in pleural adhesions.⁸ Patients with small lesions and no symptoms may be kept under observation and operation deferred until physiologic alterations require it; however, such a course should be followed only if the patient fully understands the dangers to which he is thereby exposed. Fatal pulmonary hemorrhage and intravascular clotting, which is frequent in polycythemia, are constant threats.

CASE REPORTS

Case I. A 46 year old white sales representative had had recurrent epistaxis since childhood, but aside from this annoyance his physical capacities both as a child and as a young adult seemed to be equivalent to those of his friends. At the age of 31 he was found to be anemic, and thereafter he constantly received antianemic therapy. In the ensuing years his nasal hemorrhages became increasingly severe, requiring hospitalization and multiple transfusions on three occasions. The subjective complaints of dyspnea, weakness, palpitation, pallor, loss of weight and insomnia insidiously increased in severity. The last named symptom, his chief complaint, was the result of aching pain in the extremities. This pain, which seemed to be centered in the forearms and calves, occurred only in the recumbent position and customarily awakened him. This complaint had been present in some degree for a period of eight years, but it had been particularly severe for one year. Invariably it was most severe (as were his other symptoms) when his anemia was most profound. During the initial interview the patient remarked that he had a tumor in his left chest which had been found on a routine chest film some seven or eight years previously. He had been informed that the lesion was benign and its size stationary.

The patient was a pale, asthenic male weighing 153 pounds and measuring 5 feet 10.5 inches in height. The blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. Telangiectatic lesions were present on the face, lips and tongue. Dried, encrusted blood was present in the left nares. Percussion of the heart revealed the left border to be within the midclavicular line. The cardiac rhythm was regular. The pulse rate was 96 per min. There were no cardiac murmurs. Upon auscultation over the left lung a murmur was heard at a point 5 cm. to the left of the anterior axillary line in the fifth interspace. This murmur was continuous, with both the systolic and diastolic components loudest with full inspiration. During full expiration the diastolic component disappeared and the systolic component decreased in intensity. The liver and spleen were not palpable. Clubbing of the fingers and toes was present.

Laboratory investigations included a urinalysis with normal results. The red blood cell count was 4,220,000 per milliliter, with a hemoglobin of 10 gm. per cent. The hematocrit equaled 36 per cent. A white blood cell count was 10,400, with 68 per cent neutrophil leukocytes, 3 per cent eosinophil leukocytes, 1 per cent basophil leukocytes, 28 per cent lymphocytes and 9 per cent monocytes. An examination of a blood smear disclosed the presence of a marked microcytic, hypochromic anemia. The urea nitrogen was 11.5 mg. The sedimentation rate was 9 mm./hr. The CO₂ combining power was 25 mEq/L. The circulation time was 10 sec. (Decholin).

Roentgen examination of the chest demonstrated a smoothly margined, roughly ovoid, homogeneous and sharply demarcated density in the left lower lung field which, along its medial margin, appeared to have a projection pointing toward the hilus (figure 1). The tumor mass at rest (inspiration, expiration and hold) measured on the spot film a maximum of 54.5 mm. The Valsalva procedure decreased the maximal diameter to 50 mm. The Mueller procedure increased the maximal diameter to 58 mm. (figure 2).

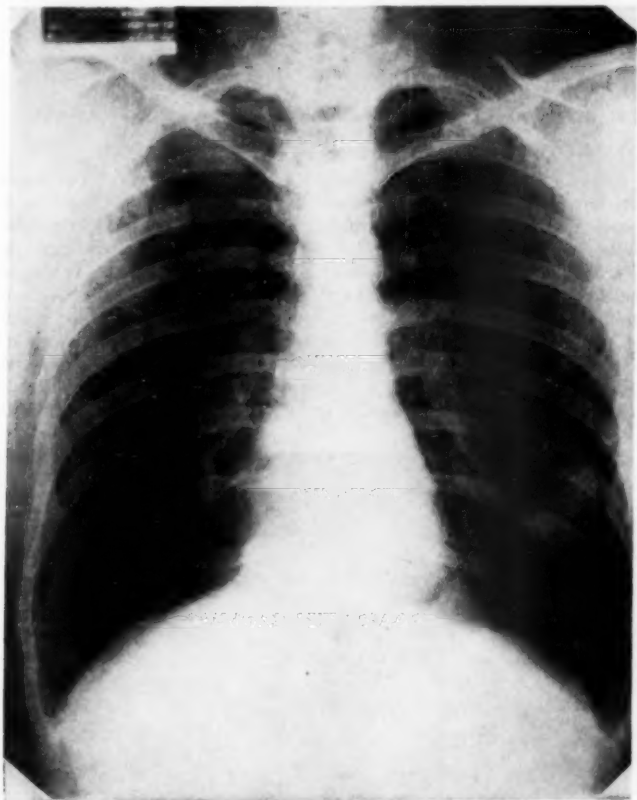


FIG. 1. Pulmonary arteriovenous fistula in the left lower lobe.

It was concluded from these studies that the patient had a pulmonary arteriovenous fistula complicating hereditary hemorrhagic telangiectasis. He was extremely debilitated. It was decided that angiocardiology would be dangerous and unnecessary. This conclusion was strengthened by the previous experience of Sisson.¹⁰

The patient was prepared for operation with 1,500 c.c. of whole blood. The left chest was entered through a long thoracotomy incision and the bed of the resected seventh left rib. There were no pleural adhesions. Palpation of the left lower lobe revealed the presence of a pulsating tumor mass measuring approximately 5 by 5 cm.,

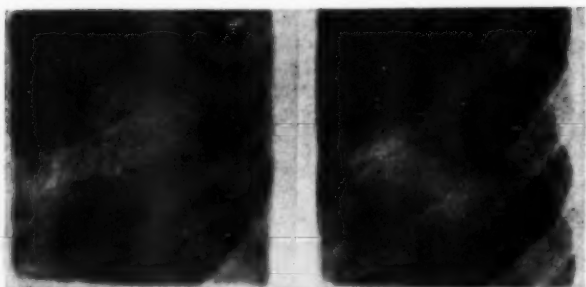


FIG. 2. Pulmonary arteriovenous fistula. Left, the Mueller procedure; right, the Valsalva procedure.

involving only the anteromedial and posterior basilar segments. The superior segment of the left lower lobe was completely free, and it is probable that a segmental resection could have been performed without difficulty; however, it was feared that anomalous vessels might be present, so the more radical procedure of left lower lobectomy was chosen. No technical difficulties were encountered. It was of interest to note the deflation of the tumor mass, which was simultaneous with the occlusion of the pulmonary artery. Immediately after removal the pathologic specimen was drained of contained blood, the vessels were retied and the pulmonary artery was injected with Lipiodol. The fistula and its connecting trunks were thus demonstrated (figure 3). Upon sectioning the lung, the pulmonary artery at a point 5 cm. from the hilus was found to be transformed into a cavity lined by gray-blue fenestrated endo-

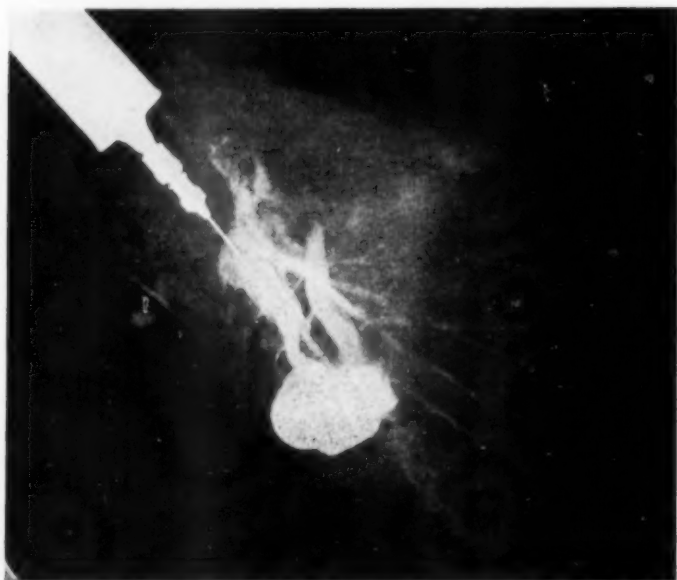


FIG. 3. Pulmonary arteriovenous fistula in the resected lobe injected with Lipiodol.

thelium. The sectioned surface of the fistula measured 5 by 3 cm. A dilated pulmonary vein was found which led directly from the cavity to the hilus. The parenchyma immediately adjacent to the lesion was violaceous and compressed (figure 4).

The postoperative course was uneventful. Since operation, the patient has been followed with serial roentgenograms of the chest (figure 5) and repeated blood

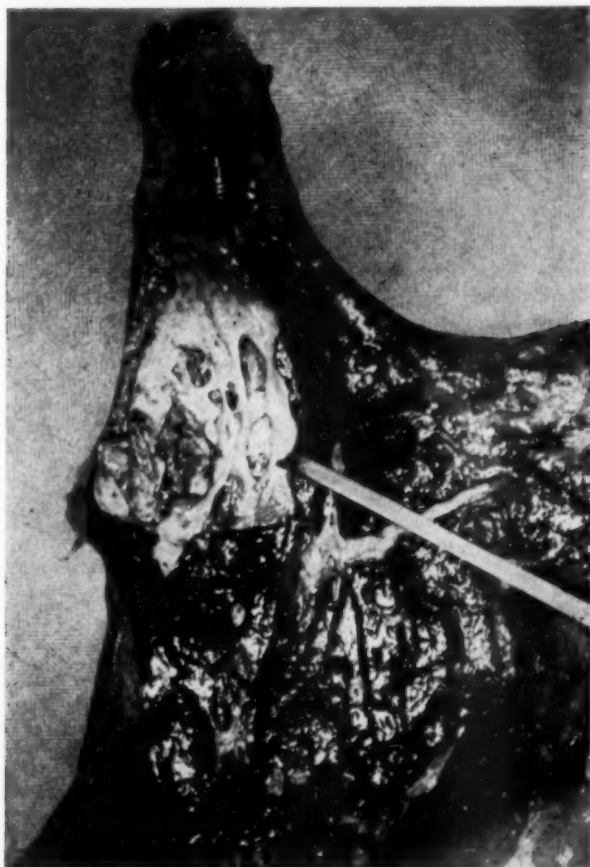


FIG. 4. The surface of the sectioned pulmonary arteriovenous fistula in the resected left lower lobe.

counts. His most recent red blood cell count was 4,540,000, with a hemoglobin of 13.8 gm. The hematocrit was 43 per cent. A smear disclosed the persistence of the hypochromic anemia, but the microcytes were greatly reduced in number. The patient has had no pain in his extremities since operation, and the remainder of his subjective symptoms are gradually disappearing. His nose bleeds have decreased from a high

of 50 per month to one or two per week, and none of his recent episodes has persisted for longer than a few minutes.

Case 2. The son of case 1, a 17 year old high school student, was examined at the request of his mother. He also had had epistaxis since childhood. His growth and development were normal in all respects, and his exercise tolerance was excellent. His subjective complaints were of frequent upper respiratory infections, epistaxis and pain in the chest. The pain was described as lancinating and localized to the left precordium. This pain occurred at irregular intervals and seemingly had no relationship to exertion.

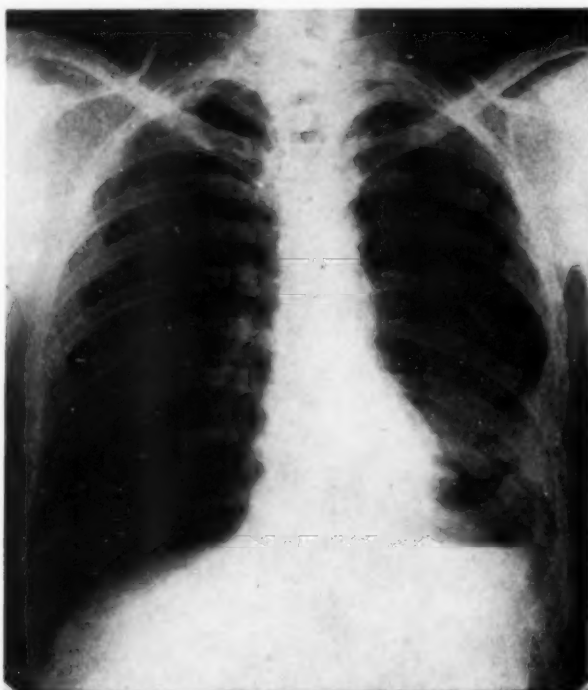


FIG. 5. Posteroanterior view of the chest three months postoperatively.

The physical examination disclosed a seemingly healthy young male measuring 5 feet 7 inches in height and weighing 140 pounds. The blood pressure was 108 mm. Hg systolic and 70 mm. diastolic. Telangiectatic lesions were present on the trunk, face, lips, tongue and nasal mucous membrane. The left cardiac border was 10 cm. to the left of the midsternal line in the fifth interspace. The pulse rate was 84 per min. The rhythm was regular. There were no cardiac murmurs. Upon auscultation of the left lung at a point 15 cm. to the left of the midsternal line in the fourth interspace, a faint systolic murmur was heard during full inspiration. The lips and nail beds were slightly cyanotic. There was no discernible clubbing of the fingers or toes. The liver and spleen were not palpable.

Laboratory investigations included a negative urinalysis. The red blood cell

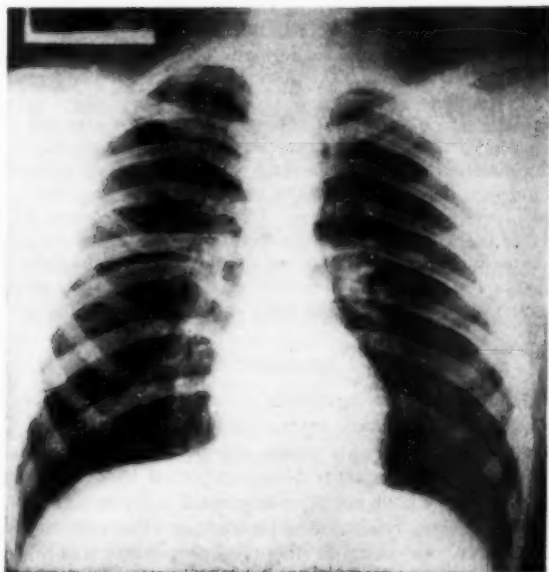


FIG. 6. Pulmonary arteriovenous fistula in the superior segment of the left lower lobe.



FIG. 7. Planogram demonstrating the vascular trunks connecting the pulmonary arteriovenous fistula and the hilus.

count was 5,030,000, with a hemoglobin of 15.8 gm. The white blood cell count was 8,000, with a normal differential. The hematocrit was 53 per cent. A blood smear revealed slight hypochromia and rouleau formation, but no immature white cells were seen. The platelet count was 150,000. Arterial blood from the femoral artery was 80.7 per cent saturated with oxygen.

Roentgenographic examination of the lungs disclosed the presence of a soft tissue density in the left midlung field overlying the anterior end of the third rib which measured approximately 1.5 cm. in diameter and was roughly circular (figure 6). Spot films taken at rest, during the Valsalva test and during the Mueller test revealed definite changes in the size of the lesion. Planography performed by Dr. Kenneth Gross demonstrated the vascular trunks connecting the lesion and the hilus (figure 7). At the conclusion of these studies it was our opinion that the diagnosis of pulmonary arteriovenous fistula was definite. Operation was advised but not urged, because of the obvious reluctance on the part of the boy's parents. We shall continue to observe his progress.

COMMENT

Hereditary hemorrhagic telangiectasis is transmitted as a dominant characteristic. The fact that pulmonary arteriovenous fistula may complicate hereditary hemorrhagic telangiectasis is being repeatedly emphasized. Pulmonary arteriovenous fistulae have been previously reported as occurring in members of a single family, but they have not been described in father and son. In neither of our cases was the classic syndrome of pulmonary arteriovenous fistula present in complete form. In one instance the clinical picture was obscured by the presence of a severe hypochromic microcytic anemia, and in the other the symptoms were not well developed. These deviations from the accepted pattern have been pointed out by Seaman and Goldman⁹ and deserve reemphasis. We believe that pulmonary arteriovenous fistula should be searched for in every instance of hereditary hemorrhagic telangiectasis. Cases may otherwise escape recognition.

Case I merits additional comment. The patient had severe aching pain in the extremities one or two hours after assuming the recumbent position. This pain was always most severe when his anemia was most profound. On two occasions it had been relieved by multiple transfusions. We have attempted to explain this phenomenon by postulating the volume of his shunt to be greater in the recumbent than in the upright position. Such an eventuality would result in a further decrease in the degree of oxygen saturation of his arterial blood. This conclusion is supported by the observation that after operation the distress disappeared entirely. It would have been of great interest to study this phenomenon by means of a continuous reading oximeter, but this apparatus was not available to us.

CONCLUSION

1. The fundamental relationship between pulmonary arteriovenous fistula and hereditary hemorrhagic telangiectasis has been reemphasized, and their important clinical characteristics have been summarized.
2. Two cases of hereditary hemorrhagic telangiectasis complicated by pulmonary arteriovenous fistula in father and son have been presented. In one instance the complicating lesion was removed by lobectomy, with cure.
3. It is urged that all cases of hereditary hemorrhagic telangiectasis be carefully examined for the presence of pulmonary arteriovenous fistula.

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CLINICAL-PATHOLOGICAL CONFERENCE *

By ROY W. SCOTT, M.D., F.A.C.P., *Cleveland*, Moderator; HOWARD B. SPRAGUE, M.D., F.A.C.P., *Boston*, JOHNSON MCGUIRE, M.D., F.A.C.P., *Cincinnati*, CHESTER S. KEEFER, M.D., F.A.C.P., *Boston*, and ALAN R. MORITZ, M.D., *Cleveland*

CLINICAL PROTOCOL

THE patient, a white unmarried female, first came under observation in January 1946 at age 27 years complaining of hoarseness and increasing breathlessness with effort over the preceding year. The family history was irrelevant. The past history was non-contributory as the patient had always enjoyed good health and was quite active in competitive athletics during school days with no cardio-respiratory limitations.

On physical examination the patient presented a normal appearance. She was well developed and well nourished and was neither dyspneic nor cyanotic. The neck veins were not distended. Examination of the eyes revealed no abnormalities. To elicit the cause of her hoarseness, noted for the past year, a laryngoscopic examination was done, and this showed a partial paralysis of the left vocal cord. The chest exhibited a normal configuration, the lungs were clear to percussion and auscultation, and the vital capacity measured 100 per cent normal. The accessible arteries showed no sclerosis and the blood pressure measured systolic 110 mm. Hg, and the diastolic 80 mm. Hg. Inspection and palpation of the precordium revealed no abnormalities.

On auscultation over the apical region the heart sounds appeared normal with no audible adventitious sounds. Over the base of the heart to the left of the sternum was heard a loud diastolic murmur lasting throughout diastole with maximum intensity in the third left interspace 2 cm. from the left sternal margin. No P_2 sound was audible, and no thrill was palpable. The aortic second sound was clear and distinct.

On fluoroscopic examination of the chest one observed the picture shown in figure 1 with the additional feature that the pulmonary arteries expanded abnormally with each cardiac systole.

The electrocardiogram (three standard limb leads) is shown in figure 2. The patient was not observed again until two years later (March 1948) and in this interval, she had continued at her work as a secretary, but stated that her respiratory limitations for effort had gradually increased and that she became cyanotic during exercise.

On this examination the patient had the same husky voice and appeared slightly cyanotic at rest. The auscultatory findings over the precordium were the same as described above as were also the fluoroscopic findings.

Examination of the blood showed R.B.C. 5,960,000, Hb. 22 grams, W.B.C. 7,000. Wassermann and Kline reactions were negative.

On January 28, 1949 right heart catheterization revealed the following pertinent data:

Pressures mm. Hg	O ₂ Vol. %
Right auricle 2/- 2	Superior cava 14.6
Right ventricle 95/3	Right ventricle 14.7
Pulmonary artery 96/53	Pulmonary artery 14.6
Femoral artery 107/72	Femoral artery 20.3

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FIG. 1.

On May 18, 1950 the patient was again examined. Although still working as a secretary, she was definitely more limited for effort and stated that ascending one flight of stairs at a normal pace caused breathlessness and cyanosis. Intermittent ankle edema was noted. Her chronic hoarseness was more marked and she was definitely more cyanotic. The lungs were clear to percussion and auscultation and the

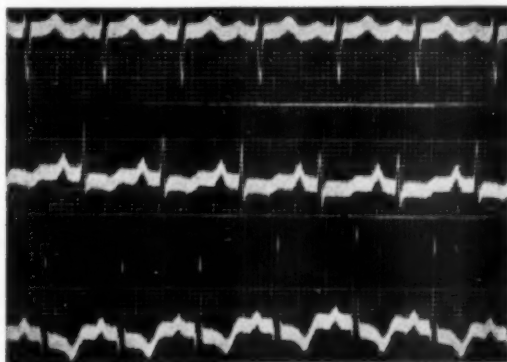


FIG. 2.

vital capacity was 90 per cent of normal. Fluoroscopic examination of the chest at this time revealed the picture shown in figure 3 with abnormal pulsations of the pulmonary arteries.

The blood findings were: R.B.C. 7,600,000; Hb. = 22.2 grams; W.B.C. 8,000; hematocrit 68%. On auscultation one heard the same loud diastolic murmur with an absent P_2 as described above.

In October 1950 the patient developed severe low back pain and vaginal examination showed a tumor the size of a large orange in the region of the right ovary. She

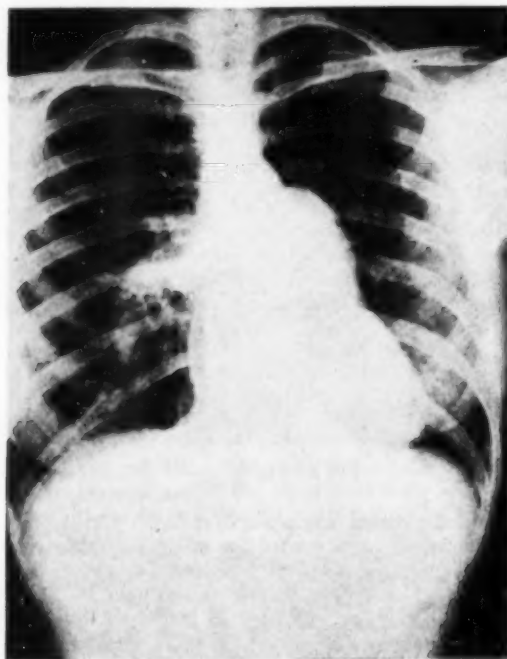


FIG. 3.

was seen by a gynecologist who advised a laparotomy which was done under spinal anesthesia supplemented by intravenous Pentothal. During the operation, the respirations became shallow and irregular and the patient died.

Dr. Scott: Members of the College and Guests: This is the first of a series of Pathological Conferences which are being presented each day in the place of one regular Panel Discussion. All are interesting cases and I trust that the remaining three will be as well attended as this one today. I will ask Dr. Sprague to open the discussion of the clinical protocol.

Dr. Sprague: The patient, a white, unmarried female, first came under observation in January 1946, at the age of 27 years, complaining of hoarseness and increased breathlessness over the preceding year. The family history was irrelevant; the past history was non-contributory as the patient had always en-

joyed good health and was quite active in competitive athletics during school days with no cardiorespiratory limitations. At this point, I would like to ask Dr. Scott if this patient had ever been ill.

Dr. Scott: I neglected to include in this protocol the fact that although unmarried, she had become pregnant about a year before her difficulty started and had had an abortion, but so far as I know, there were no complications of any kind.

Dr. Sprague: On physical examination this patient presented a normal appearance. She was well-developed and nourished and was neither dyspneic nor cyanotic. The neck veins were not distended. To elicit the cause of her hoarseness a laryngoscopic examination was done and this showed a partial paralysis of the left vocal cord. This could be explained by compression of the left recurrent laryngeal nerve from the large pulmonary artery apparent in the x-ray photograph. The chest exhibited a normal configuration; the lungs were clear to percussion and auscultation and the vital capacity measured 100 per cent normal. Apparently, therefore, there was no difficulty with the air containing elements of the lungs. The accessible arteries showed no sclerosis; the blood pressure was normal and inspection and palpation of the precordium revealed no abnormalities. Now we come to what to me is one of the most unusual features in this case, namely, the auscultatory findings. On auscultation over the apical region of the heart, the sounds appeared normal with no adventitious sounds audible. However, over the base of the heart to the left of the sternum there was a loud diastolic murmur lasting throughout diastole, the maximum intensity at the third left interspace 2 cm. from the left sternal margin. No pulmonary second sound was audible and no thrill was found. The aortic second sound was clear and distinct. On fluoroscopic examination of the chest one observed the picture shown in figure 1 with the additional feature that the pulmonary artery expanded abnormally with each cardiac systole. It would seem from the x-ray film that there was a definite increase in the hilar markings, but the periphery of the lungs appeared to be clear; therefore, the major change, so far as the circulation of the lungs was concerned, is confined to the hilar region. The electrocardiogram as produced in figure 2 is typical of right ventricular strain.

The patient was not observed again until two years later in March of 1948 and in this interval, she had continued at her work as a secretary but stated that her respiratory limitation for effort gradually increased and she became cyanotic during exercise. Thus, there has been an insidious increase in both dyspnea and in cyanosis. The cardiac auscultatory findings remained the same. The blood showed a polycythemia with increased hemoglobin content. So far as the pulmonary diastolic murmur is concerned, it seems most likely that this represents pulmonary regurgitation but I do not know how to explain the absence of the pulmonary second sound.

Dr. Keefer: I too am somewhat puzzled by the absence of the pulmonary second sound in a patient who obviously had pulmonary hypertension.

Dr. Scott: Occasionally one observes an aortic diastolic murmur due to dilatation of the aortic ring in patients with marked systemic hypertension where no aortic second sound is audible. May not the same situation exist in cases of primary pulmonary hypertension?

Dr. Keefer: I would agree with that, and I see no reason to believe that one cannot have free pulmonary insufficiency without a pulmonary second sound.

Dr. Sprague: Although the pulmonary second sound might not be heard with a stethoscope, it might have been demonstrated phonocardiographically.

Dr. Scott: I will now ask Dr. McGuire to discuss the cardiac catheterization data.

Dr. McGuire: I think the catheter data demonstrate three important aspects in this case. First, that there was marked pulmonary hypertension. The pressure in the right ventricle was systolic 95, diastolic 3 and in the pulmonary artery the systolic was 96, diastolic 53. This may be contrasted to the normal of 18 to 30 mm. of mercury in the right ventricle with a diastolic of 0 to 5 and in the pulmonary artery, systolic pressure 18 to 30, diastolic 6 to 12 mm. of mercury. The second important point is the peripheral arterial oxygen unsaturation. The oxygen content of the femoral artery was 20.3 volumes per cent and the hemoglobin was 22 grams. If this figure were multiplied by 1.3, the number of c.c. of oxygen which combine with 1 gram of hemoglobin, we have a value of 29 and this when calculated with the saturation of the pulmonary artery would give a peripheral artery saturation of only 69 volumes per cent. This type of peripheral arterial unsaturation is very important since right ventricular failure per se will not produce it. Finally, the third and important feature as revealed by the catheter data is the absence of any demonstrable left to right shunt, either interauricular or interventricular, since the oxygen content in the superior cava, the right ventricle and the pulmonary artery was essentially identical.

Dr. Scott: Dr. Sprague, will you please continue the discussion of the protocol and make your diagnosis?

Dr. Sprague: I accept the challenge, but I am not too happy about it. On May 18, 1950, the patient was again examined. Although still working as a secretary, she was definitely more limited for effort and stated that ascending one flight of stairs caused breathlessness and cyanosis. Intermittent ankle edema was noticed. The chronic hoarseness was more marked and she was definitely more cyanotic. The lungs were clear to percussion and auscultation and the vital capacity was 90 per cent of normal. Fluoroscopic examination of the chest at the time revealed the picture shown in figure 3 with abnormal pulsations of the pulmonary arteries. On auscultation one heard the same loud diastolic murmur with an absence of the pulmonary second sound. In October 1950 the patient developed severe low back pain and vaginal examination showed a tumor the size of a large orange in the region of the right ovary. She was seen by a gynecologist who advised a laparotomy which was done under spinal anesthesia supplemented by Pentothal. During the operation, the respirations became shallow and irregular and the patient died.

Now we are all agreed, I think, that this is a case of pulmonary hypertension. The question is: Is this congenital heart disease with a shunt or some primary vascular disease? Against the diagnosis of congenital heart disease is the fact that the patient was always well and active in competitive sports until her symptoms of dyspnea and hoarseness began one year before. Against the diagnosis of interauricular septal defect is the fact that the heart was not very large at the time of the first examination, and the pulmonary artery in the x-ray did not seem quite prominent enough. The late cyanosis, the hoarseness, the diastolic murmur, the enlarged pulmonary arteries are all consistent with the

Eisenmenger complex. However, the pulmonary second sound is usually accentuated in this condition. A patent ductus arteriosus with secondary lung changes I think is highly unlikely. Congenital dilatation of the pulmonary artery in itself could not produce this picture unless there were other changes in the lungs. It is very rare, and again there were no systolic murmurs. We now come to the possibility of primary vascular disease in the lung. Being in Cleveland, I am reminded of the emphasis that Dr. Scott places on the increased incidence of cor pulmonale in this area. Finally, it seems to be more likely that we deal here with one of those rare incidences of embolism of the pulmonary vessel. In two cases which I have seen similar to this, both were married and had children. In a case described by Castleman and Bland there was embolization apparently at some distant time into the tertiary radicals of the lung with free canalization. This was true in a patient of my own whose last pregnancy had been many years before. It is true that malignant disease may produce scars and emboli into the lungs and may produce the so-called *lymphangitis carcinomatosa* with secondary intravascular fibrosis which is necessary to produce cor pulmonale. This arises usually from cancer of the stomach which is unrecognized although it may have a background of several years. Rather than believing that this is primarily endarteritis of the vessels of the lungs, I am going to make the considered statement that this probably represents some strange form of embolization with perhaps some recanalization of the finer vessels of the lung. I am not at all sure that there might not be thrombosis also extending backward.

Dr. Scott: Dr. Keefer will you now please make your diagnosis?

Dr. Keefer: In the interpretation of this case, I thought the following features were outstanding: the dilated pulmonary arteries with pulmonary insufficiency; recurrent laryngeal paralysis; pulmonary hilar dance; which were later associated with polycythemia, cyanosis, arterial anoxia, right ventricular preponderance and a normal vital capacity. The common causes of a dilated pulmonary artery with a hilar dance are, of course, mitral stenosis with or without a patent foramen ovale, with congenital dilatation of the pulmonary artery and transposition of the aorta with dilatation of the pulmonary artery, high intraventricular septal defect—the Eisenmenger complex. An uncommon cause is congenital dilatation of the pulmonary artery without associated cardiac defects. I have selected for discussion the Eisenmenger complex. We have here arterial anoxia which in a patient with a dilated pulmonary artery suggests a shunt of venous blood to the arterial side. We have also pulmonary hypertension, hilar dance, pulmonary insufficiency and right ventricular preponderance. Although the catheter data demonstrated a marked increase in the systolic pressure in the right ventricle and an elevated systolic and diastolic pressure in the pulmonary artery, there was no evidence of a left to right shunt in either the auricle or the ventricle. Therefore, I would suggest that there was some over-riding of the aorta with a mixture of venous and arterial blood and a marked elevation of the pulmonary artery pressure to account for the cyanosis, polycythemia and dilated pulmonary artery. Now, if my reasoning is correct, and there is an Eisenmenger complex here, how can the murmurs be explained? I have assumed that this loud diastolic murmur arose from the pulmonary valve and was due to a marked dilatation of the artery with insufficiency. The murmurs of Eisenmenger's syndrome are complex and extremely variable. As a matter of

fact, I found there may be no murmurs recorded and that there may only be a diastolic murmur. Also in Eisenmenger's original case, only a diastolic murmur was recorded. Dr. Sprague has told us there may be both systolic and diastolic murmurs with an accentuated pulmonic second sound. From the standpoint of murmurs alone, there is nothing I can find inconsistent with the Eisenmenger complex. Now finally, one may ask the question—were there any secondary changes in the pulmonary blood vessels due to long standing pulmonary hypertension? One would certainly not be surprised to find such changes and I will make my final diagnosis: congenital heart disease with cyanosis, polycythemia, dilatation of the pulmonary artery, pulmonary insufficiency and compression of the left recurrent laryngeal nerve, transposition of the aorta with a right to left shunt of the venous blood, and secondary arteriosclerosis of the pulmonary artery. As I have assumed that this is a congenital heart lesion, I wonder whether or not this round tumor in the ovary might very well be a dermoid. I simply raise this question because that also is a congenital lesion.

Dr. McGuire: With reference to the Eisenmenger complex for which Dr. Keefer has advanced such a supporting argument, it seems to me that it is a likely probability; however, against it is the absence of any increase in oxygen in the right ventricle and the absence of a systolic murmur and a pulmonary second sound. In interauricular septal defects, either with or without mitral stenosis, certainly one would expect more oxygen in the right ventricle and in the superior cava which was not here.

A patent ductus arteriosus with reverse flow is a very rare condition but certainly theoretically might explain this x-ray. Congenital dilatation of the pulmonary artery emphasized by Oppenheimer in 1937 clinically is similar in many respects to this case. Truncus arteriosus and transposition of the great vessels are ruled out by the catheter data. Extensive pulmonary disease seems to be eliminated by the clear peripheral lung fields in the x-ray. Pulmonary endarteritis with alveolar fibrosis I suppose is something that one must still think about seriously. Primary pulmonary hypertension with a patent foramen ovale is very rarely, if ever, associated with peripheral arterial anoxia and unless there was fibrosis in the lungs and in the alveoli producing this alveolar type of block, then it seems most unlikely. Endarteritis in the pulmonary valve is almost invariably associated with the rheumatic state and with multiple other valve lesions. It seems therefore pretty improbable. We now come to the question of multiple peripheral thrombi in the branches of the pulmonary artery which are possibly secondary to primary hypertension. Here one must hypothecate some recanalization of these thrombi or possibly the functional use of tiny arteriovenous shunts, which have been described and proved to exist in the lung by Prinzmetal. However, I think that this seems far-fetched. Finally, I would say that the diagnosis is pulmonary hypertension which has been complicated, and here I agree with Dr. Sprague, with multiple pulmonary emboli, probably either primary or secondary. These latter might have followed the abortion at the time the patient was pregnant. If this be the diagnosis, then there must be some involvement of the alveoli to explain the peripheral oxygen unsaturation.

Dr. Scott: It is only fair to my good friends here on the rostrum who have tackled this problem, to tell them and you our diagnosis in this case. We felt

that we were dealing with primary pulmonary arteriolar disease with pulmonary hypertension. We thought that the loud diastolic murmur with an absent P_2 sound was due to dilatation of the pulmonary ring in the face of normal leaflets. We ascribed the arterial unsaturation to inadequate oxygenation in the alveoli due to widespread narrowing and thrombosis of the smaller pulmonary vessels.

I will now ask Dr. Moritz, our pathologist, to tell us the facts in the case.

Dr. Moritz: The ovarian tumor was a red herring. This young lady developed endometriosis and died during an operation. The important findings are, first, cor pulmonale with a 350 gram heart and when the ventricles were separated by the Marange technic, the ratio of the right ventricle wall to the left was 1.4 to 1. There was marked dilatation of the pulmonary artery, and the pulmonary valve ring measured 9 cm. in contrast to the aortic ring which measured 6 cm. Beyond the pulmonary valve ring the pulmonary arteries were still further dilated measuring 9.5 cm. and the primary and secondary branches participated in this dilatation. There was moderately severe atherosclerosis involving the intima of the large and medium sized branches of the pulmonary artery. The lungs appeared normal to gross examination save for this pulmonary atherosclerosis. On microscopic examination, however, there was a very widespread disease of the small pulmonary arteries from 100 microns in diameter and even smaller. The pulmonary vascular disease was essentially degenerative and represented marked thickening of the intima reducing the lumen to a very narrow diameter. Another type of vascular disease was observed in which the arteries were more-or-less completely occluded by proliferation of the intimal endothelium. In several sections of the lung we performed reconstruction of the pulmonary vessels and found that this was a segmental disease. Of nine vessels followed through serial sections there was only one that did not show severe obstructive resistance that ranged between 1 and 3/10 of a millimeter in length. Our interpretation of the lung findings is as follows: The changes are best explained on the basis of pulmonary thrombo-embolism, that is showers of minute emboli of solid and semi-solid material that were stopped when the vessel got to be about 100 microns in diameter. Beyond the point of obstruction, the vessel was normal and the seat of the obstruction was not more than 1 to 3 mm. in length. Dr. Sprague mentioned one of Castleman's cases similar to this which had its clinical inception just after pregnancy and Dr. Sprague has seen such a case of his own. Drysdale has recently reported such a case in the *American Journal of Medicine*. Muirhead and Montgomery have reported a case where the woman survived from four to eight pregnancies. Before we knew this girl had been pregnant, we wondered if she had had a transfusion of any kind which might have contained minute cotton fibers because such will produce a primary endarteritis, but that does not seem to be the case here. So we leave it, registering a diagnosis which seems to concur with that of Dr. Sprague and Dr. McGuire.

Dr. Scott: Well, it appears that Dr. Sprague and Dr. McGuire have a 100 per cent batting average and I want to congratulate them.

In conclusion, as the moderator of this conference, and on behalf of the American College of Physicians, I wish to thank the participants for their contribution in making it a stimulating and instructive exercise.

EDITORIAL

NEW RED CELL ANTIGENS: THEIR SIGNIFICANCE IN TRANSFUSION THERAPY

RECENT investigations have led to the discovery of a number of new antigen systems in the human red cell. With the steadily increasing employment of blood transfusions in clinical medicine it is essential that the significance of this new information be evaluated. Of primary importance is the concept of the antigen system. A period of 27 years elapsed between the discovery of the related antigens A and B and the antigens M and N. Genetic studies had already led to the development of a valid theory of inheritance of the A and B antigens. Similar studies soon revealed a specific mode of inheritance of the M and N antigens and further demonstrated complete independence of this group from the former. The concept of the antigen system, then, implies a close genetic and immunologic relationship of two or more antigens and their complete independence from other groups of antigens.

Since 1940, the date of the discovery of the Rh antigen system, at least four additional antigenic groups have been found and documented (table 1).

TABLE I

The Main Blood Group Systems: Year of Discovery and Relation to Hemolytic Reactions

System	Association with Hemolytic Transfusion Reactions
ABO (1900)	Yes (common)
MN.S (1927-1947)	Yes (rare)
P (1927)	No
Rh (1940)	Yes (common)
Kell (1946)	Yes (rare)
Lutheran (1946)	Doubtful
Lewis (1946)	Yes (very rare)
Duffy (1950)	Yes (rare)

Other groups have been reported, but have not been as extensively studied. Landsteiner's prediction regarding the individuality of human red cells seems well on its way to validation. The broader biological significance of this knowledge lies in the fact that each unrelated antigen system "tags" a different chromosome. Thus, at least eight of a total of 24 human chromosomes have been tagged. Since the antigens can be objectively demonstrated by meticulous technics and are not susceptible to environmental alteration they provide invaluable markers. As yet, linkage studies to determine other components of the tagged chromosomes have been minimally utilized, but their implications for the study of the constitutional aspects of disease are apparent.

Some blood group systems are quite simple, consisting only of two related antigens: e.g. the Duffy system, symbolized by the genes Fy^a and Fy^b ;

others are considerably more complex. The most complex and the one which has been studied most intensively is the Rh system. The Rh blood type of an individual is determined by the inheritance, from each parent, of one member of each of three pairs of related genes. These gene pairs are represented as follows: Rh_0 (D) — Hr_0 (d), rh' (C) — hr' (c), rh'' (E) — hr'' (e). An example of the use of these symbols is the following: the commonest Rh type among white Americans is $Rh_1 rh$ (Rh_0 , rh' , hr'' , hr' , hr_0 , hr'') which can also be represented CDe/cde. It has been largely as a result of the intensive investigations and explorations of the complexities of the Rh group that many of the new antigens were discovered. Most of the newer immunologic technics for detection of blood group antibodies have also resulted from these investigations. The nomenclature of the new blood group antigens has assumed a "family" character. The name has been derived either from the donor whose blood was believed to have stimulated the patient to produce the characteristic antibody or, in cases of erythroblastosis fetalis, from the family name. As is inevitable in a rapidly developing field, the discovery and characterization of new antibodies defining new red cell antigens is distinctly a matter for specialized laboratories. As new antibodies are discovered they are often temporarily identified by another label until their parallel reactions with previously described antibodies has been noted.

An important difference between the A-B-O antigen system and those more recently described lies in the fact that with the former there are regularly associated naturally occurring isoagglutinins in the sera whereas in the latter the development of antibodies invariably takes place either as a result of multiple transfusions and/or pregnancy. To attempt to assess the importance of these antigens in transfusion therapy is to raise several basic questions. Among these are: (1) In blood not specifically typed for these factors what are the chances of a patient not possessing the antigen and receiving several spaced transfusions containing the antigen? (2) What is the potency of the antigen? (3) What rôle does the immunizability of the recipient play?

These questions cannot be specifically answered for each one of the newly discovered antigens. By analogy, however, such information derived from Rh studies may be applied to other antigens. A formula for estimating the number of Rh negatives who will be immunized after three properly spaced transfusions of Rh_0 positive blood has been devised by Mollison.¹ On the basis of previous studies it has been estimated that approximately 40 per cent of Rh negative individuals will react with antibody formation if they receive three transfusions of Rh_0 (D) positive blood spaced over a period of four months or longer. On the basis of Mollison's formula, if Rh typing is not done routinely, hemolytic reactions may be expected to occur in one in 25 (0.04 per cent) of recipients who receive multiple transfusions. Similar

¹ Mollison, P. L.: *Blood Transfusion in Clinical Medicine*, 1951, C. C. Thomas, Springfield, Ill., p. 200.

calculations have been carried out for other antigens with the following results: Fy^a—0.04 per cent; S—0.03 per cent; E—0.007 per cent; Kell—0.0004 per cent. In actual practice, however, antibodies of these specificities have not been found in the sera of transfused patients in theoretically expected numbers indicating that these factors are, for the most part, not as antigenic as Rh₀ (D).

There is evidence that the Kell antigen is probably as potent as Rh₀ (D) as an antibody-producer. The opportunity for Kell iso-immunization, however, is comparatively rare (approximately one in 2500 recipients). Compatibility technics designed to detect the uncommon antibodies should provide adequate clinical safeguards. These will be discussed further below.

Variations in the capacity of recipients to form antibodies is a real but not readily assessable factor. Most evidence again has been accumulated with reference to the Rh antigens. As mentioned above, under experimental conditions, 40 per cent of Rh negative individuals who receive at least two injections of Rh₀ positive blood in a period of four months may be expected to develop Rh antibodies. Of particular interest in this regard are a handful of papers dealing with patients who have developed multiple blood group antibodies.^{2,3,4} Four were patients with acute disseminated lupus erythematosus and several had acquired hemolytic anemia. The essayist has observed several similar cases. An interesting possibility is raised regarding the "hyper-immunizability" of patients with so-called collagen diseases. Further investigation is obviously indicated.

Of practical import is the integration of these rapidly accumulating facts into the everyday clinical use of blood for transfusion. Most serious hemolytic reactions are still probably due to A-B-O incompatibility or Rh incompatibility. In regard to the former, technical procedures are well established and standardized and investigation usually reveals that errors are due to the human factor. In regard to Rh antigens improvements in technical methods have been but tardily incorporated into clinical use. Routine Rh typing is now fairly well established as a blood bank procedure. A few comments regarding this procedure may be pertinent. Since the Rh₀ (D) antigen is the most potent producer of antibodies, routine typing is most commonly done with an anti-Rh₀ (D) serum and individuals divided into Rh₀ (D) positive and Rh₀ (D) negative categories. The latter, as recipients, should always receive Rh₀ (D) negative blood. But Rh₀ (D) negative donors need further screening. Approximately 2 per cent of American whites are of types rh' (C) or rh'' (E). Individuals of these types are Rh₀ (D) negative. The antigens rh' (C) and rh'' (E) are not potent antibody producers,

² Callendar, S. T., and Race, R. R.: A serological and genetical study of multiple antibodies formed in response to blood transfusion by a patient with lupus erythematosus diffusum, *Ann. Eugen.* 13: 102, 1946.

³ Collins, J. O., Sanger, R., Allen, F. H., and Race, R. R.: Nine blood group antibodies in a single serum following multiple transfusions, *Brit. M. J.* 1: 1297, 1950.

⁴ Baldwin, G. B.: Acute disseminated lupus erythematosus with report of a fatal case, *M. J. Australia* 2: 11, 1945.

yet it is probably advisable to screen Rh₀ (D) negative donors with anti-C and anti-E sera to avoid using such blood if possible. Of even greater import is the variant of Rh₀ (D) known as D^a. Approximately 2 per cent of American negroes and 1 per cent of American whites possess this antigen. With most anti-Rh₀ (D) sera these individuals will be typed as Rh₀ (D) negative. Only by subsequently performing a Coombs' test on their blood will it be ascertained that they are of type D^a. The D^a variant although difficult to detect by ordinary typing is a potent antigen and can lead to antibody production in the recipient.

It is now definitely established that blood group antibodies exist in several forms and that the time honored method of cross-matching in physiologic saline solution is no longer adequate. To detect so-called incomplete agglutinins a variety of methods has been proposed. The simplest and most accurate for routine use is probably the method employing 20 per cent bovine albumin solution for suspension of donor cells instead of normal saline solution. The advantage of this method lies in the fact that not only will it detect incomplete antibodies of the Rh variety but of other specificities as well. Detection of incompatibility will be facilitated and compatible blood can be found. The specificity of the antibody can be established by laboratories specially equipped to study such problems. This need not delay the administration of the needed blood.

It is indeed fortunate that, coincident with the increasing knowledge of the complexity of the red cell antigenic structure and the increasing use of blood transfusions, a more rational physiologic approach to the management of hemolytic transfusion reactions associated with anuria has occurred. Since the clarification of the pathologic physiology of lower nephron nephrosis current therapy has been characterized by a limited fluid intake and the supplying of caloric requirements by carbohydrate and fat until adequate output occurs. In this regard, Bull et al.⁵ have recently recommended the supplying of fluids and calories through an indwelling polythene gastric tube employing a mixture of glucose (400 gm.), peanut oil (100 gm.) and water (1 liter) per 24 hours. The use of other measures such as splanchnic block, renal decapsulation, and the "artificial kidney" is rarely indicated.

MILTON S. SACKS, M.D.

⁵ Bull, G. M., Joekes, A. M., and Lowe, K. G.: Conservative treatment of anuric uremia, *Lancet* 2: 229, 1949.

CLINICAL PATHOLOGICAL CONFERENCES

Comment from readers of the ANNALS is invited by the Editor on the proposal to include Clinical Pathological Conferences in the material published by this journal. A trial publication of such a Conference is included in this number.

REVIEWS

The Treatment of Diabetes Mellitus. 9th ed. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., Sc.D., and ALEXANDER MARBLE, A.M., M.D. 771 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1952. Price, \$12.00.

The long enjoyed prestige of this work is well known and it needs little recommendation to the English reading world of internists and other students of diabetes. Unlike most new editions, this is actually slenderer than its predecessor of 1946 and is shorter by some 30 pages despite an increased content. This has been achieved by the use of thinner paper and a larger type area per page. The result is a book of convenient size for easy reading and handling.

The data in this volume are based on the authors' unique experience in handling over 40,000 diabetic patients. An indication of the scope and range of their experience may be gained from statistics in their chapter on juvenile diabetes. When writing on this subject they can summon the knowledge won with over 3000 children observed over a period of 53 years: 82 per cent of these were living at a follow-up survey a short time before publication of the current edition, less than 1 per cent were untraced, and 72 of the once juvenile patients were over 40 years of age.

The chapters written by Dr. Joslin himself are in his own informal and engaging style. The authors show a missionary zeal to convert both the diabetic and his doctor alike to the wisdom of faultless diabetic control. They stress therefore not only advances in treatment but also the complications which result from inadequate care.

The present edition has been thoroughly revised and statistics brought up to date. New developments have been incorporated, as, for example, the use of NPH insulin, and the inclusion of claims for vitamin B₁₂ and for BAL in the treatment of diabetic neuritis. A large number of references subsequent to 1946 have been added to the bibliography.

The book remains indispensable to every student of diabetes.

H. J. L. M.

Cardiac Therapy. By HAROLD J. STEWART, M.D., Associate Professor of Medicine, Cornell University Medical College, New York. 622 pages; 18 × 26 cm. Paul B. Hoeber, Inc., New York. 1952. Price, \$10.00.

This is a detailed and comprehensive book on the treatment of disorders of the heart. Since therapy, to be properly applied, should be based upon an understanding of the disease which is being treated, the author includes in many instances a discussion of the pertinent clinical and other aspects of the condition. His approach is generally a sound one. The material, methods and recommendations are up-to-date. The bibliography is helpful. Advice is specific and complete and practical.

This text should prove useful to all who have occasion to treat patients with heart disease.

S. S.

Expert Committee on Mental Health: Alcoholism Subcommittee, Second Report. World Health Organization Technical Report Series No. 48. 39 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available in U. S. A. through Columbia University Press, International Documents Service, New York. Price, 25 cents.

This new technical report on alcoholism presents such sound, up-to-date thinking on this difficult medical-psychological problem that it is highly recommended to any

physician who is concerned with, or who wishes to inform himself about, the practical aspects of alcoholism.

In a sense it presents its material in the reverse of logical order, because it starts with a thorough description of various practical methods of treatment and rehabilitation for the various categories and ends in two annexes, which are very important, with excellent descriptions of various types of alcoholics, the phases of alcoholic addiction and the differential diagnosis between an alcohol addict and other excessive drinkers.

The section on rehabilitation describes intramural as well as out-patient treatment, what types are most suitable for each, under what auspices intensive psychotherapy can best be supplied, and the relative costs of these measures. Also in this section is a detailed discussion of the use of disulfiram (tetraethylthiuram disulfide) commonly known as Antabuse, Aversol or Refusal. The indications, contraindications, dosages and dangers are discussed.

This report stresses the need for more accurate surveys of prevalence and indicates steps to accomplish this. It analyzes data already accumulated and concludes that, "the extent of alcoholism is consistently underestimated by health administrations in most countries. In many countries adult males in need of treatment for alcoholism outnumber those in need of treatment for tuberculosis by several hundred per cent. The concealed cost of alcoholism to many countries is enormous. The rehabilitation of these alcoholics therefore costs the community much less than leaving them untreated or handling them by penal measures."

H. W. N.

Side Effects of Drugs. By L. MEYLER, Consulting Physician at Groningen (Netherlands); translated by PH. VUIJSJE and W. MULHALL CORBET, Amsterdam. 268 pages; 15.5 x 23.5 cm. Elsevier Publishing Co., New York. 1952. Price, \$5.50.

This book has been written to describe the unusual reactions that may follow the administration of drugs. The well-recognized untoward effects are only briefly stated. The author points out that the side effects that rarely occur are usually not described in the literature. Therefore only a careful study of the literature, hospital records and long experience in prescribing drugs could provide the data necessary for a summary of this type. Numerous references are given at the end of each of the 25 chapters. The material covered in the text appears to be adequate and the index is extensive so that an individual drug can be found quickly.

In the preface, noting that there is a great tendency to rely too much on chemotherapy, the author pleads for a more critical attitude in the prescribing of drugs,— "no drug unless definitely indicated. Diagnosis first, treatment afterwards."

As a supplement to the usual texts on pharmacology and toxicology the book will be welcomed by physicians.

C. J. C.

Roentgen-Diagnostics (Volume II, Skeleton, Part 2). By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, and E. UEHLINGER. First American Edition (based on the Fifth German Edition, revised and enlarged); English translation arranged by JAMES T. CASE, M.D., D.M.R.E., Professor of Radiology Emeritus, Northwestern University School of Medicine. 1190 pages; 19 x 28 cm. (boxed). Grune and Stratton, New York. 1952. Price, \$45.00.

Roentgen-Diagnostics is the English edition of the *Lehrbuch der Roentgen Diagnostik*, which for many years has been the most outstanding radiologic text and reference book. The translation of this outstanding German work was arranged and edited by Dr. James T. Case.

Volume II of this publication is a continuation of Volume I, which is devoted mainly to the roentgen examination and diseases of the skeletal system. Each chapter deals with those diseases of bone with common or similar etiologies. Roentgenologic diagnosis of the vertebral column and the skull and its contents are dealt with rather extensively in separate chapters. Another chapter is devoted to associated diseases of the muscles, tendons and vascular system. The last chapter is concerned with the differential diagnosis of the more important diseases discussed in both Volumes I and II.

The bone lesions are thoroughly discussed from a clinical and pathological standpoint, but the emphasis is on the roentgen considerations. Each disease is beautifully illustrated with roentgenograms, clinical photographs, diagrammatic sketches and charts. In the sections on the vertebral column and skull, not only are the pathological lesions discussed, but the normal anatomy and roentgen technics are also given thorough consideration. The bibliography at the end of each chapter is very complete.

This great publication is translated in such a fashion as to be easily read and understood and will be of great value to all medical specialists.

J. M. D.

Antoine Lavoisier: Scientist, Economist, Social Reformer. By DOUGLAS McKIE, D.Sc., Ph.D. 440 pages; 14 × 21.5 cm. Henry Schuman, New York. 1952. Price, \$6.00.

The life of Lavoisier was replete with industry, romance and science. Dr. Douglas McKie has made all of these facets of the great Frenchman live in the pages of his book, "Antoine Lavoisier: Scientist, Economist, Social Reformer."

The writer has a felicity of diction which holds one's attention throughout the biography. He has captured the significance of the overthrow of the phlogiston theory by Lavoisier and pointed out how this iconoclastic act laid the foundation stones of modern chemistry. As overtones in the running account of the busy life of Lavoisier, one hears the dissonant crescendo of the drums of the revolution, ultimately terminating in the guillotining of the great scientist Lavoisier.

As one reads the pages, it scarcely seems possible that one man could have piled so much into a short life of 50 years, as did Lavoisier.—Commissioner of Gunpowder, concerned with the lighting of Paris, a member of the Commission on Weights and Measures, experimenter in the National Academy, and unfortunately a member of the Farmers-General, which brought to him an unwarranted and untimely doom on the guillotine.

The book fittingly closes with the timeless statement of Lagrange to Delambre: "Only a moment to cut off that head and a hundred years may not give us another like it."

J. C. K., Jr.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

American Pocket Medical Dictionary: A Dictionary of the Principal Terms Used in Medicine, Nursing, Pharmacy, Dentistry, Veterinary Science, and Allied Biological Subjects. 19th Ed. 639 pages; 17.5 × 12 cm. (limp leather binding). 1953. W. B. Saunders Company, Philadelphia. Price, \$3.25 plain; \$3.75 with thumb-index.

- The Anatomy of the Nervous System: Its Development and Function.* 9th Ed. By STEPHEN WALTER RANSON, M.D., Ph.D., Late Professor of Neurology and Director of Neurological Institute, Northwestern University Medical School, Chicago; revised by SAM LILLARD CLARK, M.D., Ph.D., Professor of Anatomy, The Vanderbilt University School of Medicine, Nashville. 581 pages; 25.5 × 17 cm. 1953. W. B. Saunders Company, Philadelphia. Price, \$8.50.
- An Atlas of Skull Roentgenograms.* By BERNARD S. EPSTEIN, M.D., Associate Radiologist, The Jewish Hospital of Brooklyn, Brooklyn, New York; and LEO M. DAVIDOFF, M.D., Neurosurgeon, to the Mount Sinai Hospital, New York City, etc. 415 pages; 26 × 18 cm. 1953. Lea & Febiger, Philadelphia. Price, \$15.00.
- BCG Vaccination: Studies by the WHO Tuberculosis Research Office, Copenhagen. Monograph Series No. 12.* Report prepared under the direction of LYDIA B. EDWARDS, M.D., Chief of Field Studies, and CARROLL E. PALMER, M.D., Ph.D., Director, with the assistance of KNUT MAGNUS, cand. act., Assistant Statistician, Tuberculosis Research Office, World Health Organization, Copenhagen. 307 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$3.00.
- Bedside Diagnosis.* 2nd Ed. By CHARLES SEWARD, M.D., F.R.C.P. (Edin.), Honorary Physician, Royal Devon and Exeter Hospital, etc.; with a Foreword by SIR HENRY COHEN, M.D., F.R.C.P., Professor of Medicine, University of Liverpool. 380 pages; 19 × 12.5 cm. (limp leather binding). 1952. The Williams & Wilkins Company, Baltimore. Price, \$3.50.
- Danger Signals: Warnings of Serious Diseases.* By WALTER C. ALVAREZ, M.D., Consultant in Medicine, Emeritus, Mayo Clinic. 176 pages; 22.5 × 15 cm. (paper-bound). 1953. Wilcox & Follett Company, Chicago. Price, \$3.00.
- Elementary Statistics with Applications in Medicine.* By FREDERICK E. CROXTON, Ph.D., Professor of Statistics, Columbia University. 376 pages; 22 × 14.5 cm. 1953. Prentice-Hall, Inc., New York. Price, \$10.00.
- Endocrine Treatment in General Practice.* Edited by MAX A. GOLDZIEHER, M.D., and JOSEPH W. GOLDZIEHER, M.D. 474 pages; 23.5 × 15.5 cm. 1953. Springer Publishing Company, New York. Price, \$8.00.
- The Essentials of Medical Diagnosis: A Manual for Students and Practitioners.* 2nd Ed. By RT. HON. LORD HORDER, G.C.V.O., M.D., F.R.C.P. (Lond.), Extra Physician to H. M. the Queen, etc.; and A. E. GOW, M.D., F.R.C.P. (Lond.), Honorary Physician to Household, H. R. H. the Duchess of Kent, etc.; Second Edition revised with the assistance of RONALD BODLEY SCOTT, M.A., D.M. (Oxon), F.R.C.P. (Lond.), Physician to M. H. Household, etc. 462 pages; 19 × 12.5 cm. 1953. The Williams & Wilkins Company (A William Wood Book), Baltimore. Price, \$6.00.
- Famine Disease in German Concentration Camps: Complications and Sequels, with Special Reference to Tuberculosis, Mental Disorders and Social Consequences. Acta Psychiatrica et Neurologica Scandinavica Supplementum 83.* By PER HELWEG-LARSEN, HENRIK HOFFMEYER, JØRGEN KIELER, EIGIL HESS THAYSEN, JØRN HESS THAYSEN, PAUL THYGESEN and MUNKE HERTTEL WULFF. 460 pages; 24 × 16.5 cm. (paper-bound). 1952. Ejnar Munksgaard, Copenhagen. Price, Dan. kr. 35.00.

Fundamentals of Clinical Cancer, with Emphasis on Early Diagnosis and Treatment.

By LEONARD B. GOLDMAN, M.D., Clinical Professor of Radiotherapy, New York Medical College, Flower and Fifth Avenue Hospitals, etc. 312 pages; 26 × 17.5 cm. 1953. Grune & Stratton, New York. Price, \$8.75.

Gastric Cancer. By ALFRED H. IASON, M.D., Attending Surgeon, Adelphi Hospital, etc.; illustrations by ALFRED FEINBERG, Instructor of Medical Illustration, Department of Pathology, College of Physicians and Surgeons, Columbia University, New York City. 316 pages; 26 × 17.5 cm. 1953. Grune & Stratton, New York. Price, \$7.50.

Gifford's Textbook of Ophthalmology. 5th Ed. By FRANCIS HEED ADLER, M.D., Professor of Ophthalmology, University of Pennsylvania Medical School, etc. 488 pages; 24 × 15.5 cm. 1953. W. B. Saunders Company, Philadelphia. Price, \$7.50.

Liver Injury: Transactions of the Eleventh Conference, April 30 and May 1, 1952, New York, New York. Edited by F. W. HOFFBAUER, M.D., Associate Professor, Department of Medicine, University of Minnesota Hospitals, Minneapolis, Minnesota. 265 pages; 23.5 × 15.5 cm. 1953. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$4.00.

A Manual of Clinical Allergy. By JOHN M. SHELDON, M.D., Professor of Internal Medicine, University of Michigan Medical School, etc.; ROBERT G. LOVELL, M.D., Instructor in Internal Medicine, University of Michigan Medical School; and KENNETH P. MATHEWS, M.D., Assistant Professor of Internal Medicine, University of Michigan Medical School. 413 pages; 25.5 × 16.5 cm. 1953. W. B. Saunders Company, Philadelphia. Price, \$8.50.

1953 Medical Progress: A Review of Medical Advances During 1952. MORRIS FISHEIN, M.D., Editor. 301 pages; 23.5 × 15.5 cm. 1953. The Blakiston Company, New York. Price, \$5.00.

Osteosklerose und Knochenmarkfibrose. By RUDOLF STODTMEISTER and STEFAN SANDKÜHLER; with x-ray assistance of ALBERT LAUR. 135 pages; 24.5 × 17.5 cm. 1953. Georg Thieme Verlag, Stuttgart; Agents in U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 28.50.

Poliomyelitis. By W. RITCHIE RUSSELL, C.B.E., M.D. (Edin.), M.A. (Oxon), F.R.C.P. (Edin.), F.R.C.P. (Lond.), Consultant Neurologist to the United Oxford Hospitals, etc. 84 pages; 22 × 14 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, \$3.00.

The Principles of Neurological Surgery. 4th Ed. By LOYAL DAVIS, M.S., M.D., Ph.D., D.Sc. (Hon.), Professor of Surgery and Chairman of the Division of Surgery, Northwestern University Medical School, Chicago, Illinois. 544 pages; 24 × 15.5 cm. 1953. Lea & Febiger, Philadelphia. Price, \$8.50.

Second Annual Report on Stress. By HANS SELYE, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), Professor and Director of the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, and ALEXANDER HORAVA, M.D. (Lausanne), Research Associate and Librarian of the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal. 526 pages; 25.5 × 17.5 cm. 1952. Acta, Inc., Medical Publishers, Montreal. Price, \$10.00, plus 34¢ mailing charges.

- Symptoms and Signs in Clinical Medicine: An Introduction to Medical Diagnosis.* 5th Ed. By E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., Senior Lecturer in Medicine, University of Liverpool, etc. 480 pages; 22.5 × 14 cm. 1952. The Williams & Wilkins Co., Baltimore. Price, \$8.00.
- Synovial Fluid Changes in Joint Disease.* By MARIAN W. ROPES, M.D., Associate Physician, Massachusetts General Hospital, etc.; and WALTER BAUER, M.D., Chief of Medical Services, Massachusetts General Hospital, etc. 150 pages; 24.5 × 16 cm. 1953. Published for the Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. Price, \$4.00.
- Taschenbuch der Praktischen Medizin.* Edited by JOHANNES KOTTMAIER, Baden-Baden. 937 pages; 19.5 × 12 cm. 1953. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzl. DM 29.70.
- Textbook of Virology for Students and Practitioners of Medicine.* 2nd Ed. By A. J. RHODES, M.D., F.R.C.P. (Edin.), Research Associate, Connaught Medical Research Laboratories, and Professor of Virus Infections, School of Hygiene, University of Toronto, etc.; and C. E. VAN ROOYEN, M.D., D.Sc. (Edin.), M.R.C.P. (Lond.), Research Member, Connaught Medical Research Laboratories, and Professor of Virus Infections, School of Hygiene, University of Toronto, 561 pages; 23.5 × 15.5 cm. 1953. The Williams & Wilkins Company, Baltimore. Price, \$8.00.
- Treatment of Mental Disorder.* By LEO ALEXANDER, M.D., Director, The Neurobiological Unit, Division of Psychiatric Research, Boston State Hospital, etc. 507 pages; 25.5 × 16.5 cm. 1953. W. B. Saunders Company, Philadelphia. Price, \$10.00.

COLLEGE NEWS NOTES

NEW LIFE MEMBERS

The College announces with pleasure that the following Fellows have become Life Members of the American College of Physicians since the publication of last month's issue of this journal:

Dr. Laurence A. Grossman, Nashville, Tenn.
Dr. Frank LaM. Jennings, Indianapolis, Ind.
Dr. Martin Marcel Kirshen, Chicago, Ill.
Dr. Steven O. Schwartz, Chicago, Ill.
Dr. Lawrence M. Serra, Baltimore, Md.
Dr. Richard Nelson Kent, Fort Wayne, Ind.
Dr. Frank R. Barta, Sr., Omaha, Nebr.
Dr. Hugh P. Greeley, Boston, Mass.
Dr. Otis G. King, Bluefield, W. Va.
Dr. Norman B. Roberg, Chicago, Ill.
Dr. Trevor G. Browne, Phoenix, Ariz.
Dr. Wilson Fitch Smith, Hartford, Conn.
Dr. J. LaMonte Zundell, Oakland, Calif.
Dr. Paul H. Rowe, Minot, N. D.
Dr. Arless A. Blair, Fort Smith, Ark.
Dr. Arthur C. Clasen, Kansas City, Mo.
Dr. Robert N. Hedges, Chicago, Ill.
Dr. Louis H. Landay, Pittsburgh, Pa.
Dr. William J. Armstrong, Butler, Pa.
Dr. Alex F. Robertson, Jr., Staunton, Va.
Dr. LeRoy H. Sloan, Chicago, Ill.
Dr. W. Raney Stanford, Durham, N. C.
Dr. Herbert V. Dobson, Peterborough, Ont., Can.
Dr. Mayer A. Green, Pittsburgh, Pa.

A. C. P. COMMITTEE ON EDUCATIONAL POLICY ENLARGED

The Committee on Educational Policy of the College has been enlarged to five members, consisting of Drs. M. A. Blankenhorn, Cincinnati, Chairman; Edward L. Bortz, Philadelphia; Harold H. Jones, Winfield; Maurice C. Pincoffs, Baltimore; and Cyrus C. Sturgis, Ann Arbor. The Committee has been relieved of duty with the Committee on Postgraduate Courses, and has been instructed by the Board of Regents to undertake, with the aid of the Executive Secretary, a systematic collection of the evidences of membership satisfaction or dissatisfaction with the program of the Annual Sessions, to analyze these and submit a report to the Consulting Committee on Annual Sessions.

A. C. P. POSTGRADUATE COURSES

Four courses on the Spring Schedule of 1953 have been concluded with very gratifying success. Course No. 1, PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE, directed by Dr. A. Carlton Ernstene, F.A.C.P., at the Cleveland Clinic Foundation, had a registration of 77 physicians; Course No. 2, STUDIES IN THE CLINICAL ASPECTS AND DIAGNOSTIC

PROCEDURES IN CARDIOVASCULAR DISEASES, directed by Dr. George C. Griffith, F.A.C.P., at the University of Southern California School of Medicine, had a registration of 34 physicians; Course No. 3, INTERNAL MEDICINE: SELECTED SUBJECTS, directed by Dr. David P. Barr, F.A.C.P., at Cornell University Medical College, had a registration of 72 physicians, and Course No. 4, INTERNAL MEDICINE—SELECTED SUBJECTS, directed by Drs. Hugh R. Butt, F.A.C.P., Arlie R. Barnes, F.A.C.P., Edgar V. Allen, F.A.C.P., and William H. Dearing, F.A.C.P., at the Mayo Clinic and Foundation, had a registration of 70 physicians. In the case of Course No. 4, a great many applicants were turned away because the size of the class could not be increased.

The following courses are yet to be given on the Spring Schedule:

No. 5—CARDIOVASCULAR DISEASES, 1953

William G. Leaman, M.D., F.A.C.P., Director; Philadelphia Institutions, Philadelphia, Pa.

(6 days—April 27-May 2, 1953)

No. 6—CONTROVERSIAL ISSUES IN INTERNAL MEDICINE

Garfield G. Duncan, M.D., F.A.C.P., Director; The Pennsylvania Hospital, Philadelphia, Pa.

(5 days—May 11-15, 1953)

No. 7—ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION

Conger Williams, M.D. (Associate), Director; Massachusetts General Hospital, Boston, Mass.

(6 days—May 11-16, 1953)

(This course is filled to capacity.)

No. 8—INTERNAL MEDICINE: IMPORTANT REFINEMENTS IN DIAGNOSIS AND TREATMENT

Howard P. Lewis, M.D., F.A.C.P., Director; University of Oregon School of Medicine, Portland, Ore.

(5 days—May 18-22, 1953)

Fees for the courses that are open are \$30.00 to members; \$60.00 to non-members. Full outlines of the Faculties and of the daily programs, with registration forms, may be obtained from the Executive Offices, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

The Postgraduate Course Schedule for the Autumn of 1953 will be available by May 1.

A. C. P. REGIONAL MEETINGS

The following Regional Meetings of the College have been held since the beginning of 1953:

EASTERN PENNSYLVANIA, at Philadelphia, January 16; Dr. Thomas M. McMillan, F.A.C.P., Governor and General Chairman; Dr. Alex. M. Burgess, F.A.C.P., Providence, special guest speaker. Attendance, 300.

COLORADO, at Denver, February 17; Dr. C. F. Kemper, F.A.C.P., Governor; Dr. Frank T. Joyce, F.A.C.P., Chairman of Program Committee; Dr. Howard P. Lewis, F.A.C.P., Portland, special guest speaker. Attendance, 130.

VIRGINIA, at Old Point Comfort, February 26; Dr. Charles M. Caravati, F.A.C.P., Governor; Dr. William A. Read, F.A.C.P., Chairman, Committee on Local Arrangements; Dr. Wallace M. Yater, F.A.C.P., Washington, special guest speaker. Attendance, 120.

- DELAWARE, at Wilmington, February 27; Dr. Lemuel C. McGee, F.A.C.P., Governor; Dr. C. A. D'Alonzo, F.A.C.P., Chairman, Committee on Arrangements; Dr. John Minor, F.A.C.P., Washington, and Dr. George H. Lathrope, F.A.C.P., Morristown, special guest speakers. Attendance, 65.
- NEBRASKA, at Omaha, February 28; Dr. Joseph D. McCarthy, F.A.C.P., Governor; Drs. M. H. Brodkey, F.A.C.P., and A. M. Greene, F.A.C.P., Program Committee; Dr. T. Grier Miller, F.A.C.P., President of the College, special guest speaker. Attendance (estimated), 90.
- SOUTHERN CALIFORNIA, at Los Angeles, March 7; Dr. Leland Hawkins, F.A.C.P., Governor; Dr. George C. Griffith, F.A.C.P., Program Chairman and Course Director; Dr. Henry L. Bockus, F.A.C.P., Philadelphia, special guest speaker. The program consisted of a Symposium on Cardiac Resuscitation and presentations on "Gitaligin," "Oral Mercurial Diuretics" and "Auricular Arrhythmias." It was the closing program of the American College of Physicians Postgraduate Course in Cardiovascular Disease, given under the auspices of the College and the directorship of Dr. Griffith. Attendance (estimated), 75.
- NEW ENGLAND—MAINE, VERMONT and NEW HAMPSHIRE, at Hanover, March 14; Dr. Richard S. Hawkes, F.A.C.P., Governor for Maine; Dr. E. L. Amidon, F.A.C.P., Governor for Vermont; Dr. Harry T. French, F.A.C.P., Governor for New Hampshire, and General Chairman; Dr. Chester S. Keefer, F.A.C.P., Governor for Massachusetts, special guest speaker. Attendance (estimated), 75.
- KANSAS, at Kansas City, March 20; Dr. William C. Menninger, F.A.C.P., Governor; Dr. Lee H. Leger, F.A.C.P., Chairman, Program Committee; Dr. Walter L. Palmer, F.A.C.P., Regent, special guest speaker, "Medicine—Historical and Global Reflection." Attendance (estimated), 75.
- SOUTHERN ILLINOIS, at Bloomington, March 21; Dr. Charles H. Drenckhahn, F.A.C.P., Governor; Dr. Edgar M. Stevenson, F.A.C.P., General Chairman; Dr. Howard Wakefield, F.A.C.P., Governor for Northern Illinois, special guest speaker. Attendance (estimated), 70.

PROGRESS REPORT—A. C. P. GROUP INSURANCE PLANS

As of March 1, 1953, more than one-half of the eligible members of the College has subscribed to the Health and Accident Plan. If applications continue coming in at the present rate, it appears probable that the necessary number will be in our Association Service Office on or about April 1, 1953. It is required that 51% of the eligible members subscribe, and the initial subscription period was set for sixty days. It is possible that the Plan may be held open for an additional sixty days, but those who have delayed to send in their subscriptions should do so immediately, not only for their own benefit, but for that of the rest of the College members. The larger the percentage of subscription, the more favorable will be the experience of the Plan, with greater possibilities for extension of even more benefits than originally provided.

The College Health and Accident Plan provides protection up to five years for illness and up to life for accident. Most other group plans are limited to two years' benefits. The Educators Mutual Life Insurance Company, carriers of the Health and Accident Plan for the College, in the master policy has accepted service in all states or territories in which College members reside, which provides legal protection should any member not be satisfied with any decision of the carrier or of the Arbitration Committee. Members who already carry health and accident insurance may also carry at the same time, if they desire, the College Health and Accident Policy, because

benefits are not prorated. Furthermore, members who do not want to duplicate present coverage may subscribe to the College Plan, subject to the policy becoming effective at the expiration date of their present policy. However, subscriptions should be sent in now, postdated to the time the College policy shall become effective.

All Fellows and Associates who have not passed their seventieth birthday and who are still in active work, not presently with the Armed Forces, are eligible. Their past health record may cause the underwriters to limit their participation to \$50.00 or \$75.00 per week, rather than the maximum of \$100.00 per week, but such members cannot be denied the right to participate. The A. C. P. Health and Accident Plan is in no way tied in with the Professional Liability (malpractice) Plan and may be secured without applying for the malpractice insurance. Each Plan is independent of the other and may be secured without reference to the other.

A representative number of the members of the College have already subscribed to the Professional Liability (malpractice) Group Plan, and the insurance is already in effect, because there is no regulation requiring, in this case, a certain percentage of participation. Therefore, the protection is effective upon receipt of the application and check, and the Certificate is immediately issued to the member. So many applications have already been received that the College Brokers have been authorized to increase the limits of coverage to \$50,000/\$150,000 protection. Only Fellows and Associates, and in some cases their employees, may be insured under this policy. Partnerships and Clinics, composed of both members and non-members of the College, are individually underwritten at rates lower, in most cases, than may be secured from outside sources. Our Professional Liability Plan provides for reductions in premium if this group proves, as we expect it will, to be a select group with few suits. It also provides for larger reductions based upon a large participation by our members. The more that join, the lower our rates will become.

Members who have sent in their applications and checks for the Health and Accident Plan are entitled to protection at the very earliest moment possible. If those who have procrastinated for one reason or another will send in their applications now, it will redound to the benefit of all. Applications with a future effective date count toward qualifying the Plan immediately.

A monthly report of progress on the College Plans will be made. The Association Service Office, 1500 Walnut Street, Philadelphia 2, Pa., is attending to all details and furnishing information and forms.

COMING EXAMINATIONS BY CERTIFYING BOARDS

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa.

Oral Examinations—Philadelphia, Pa., May 1-3, 1953.

FUTURE MEETING, AMERICAN GOITER ASSOCIATION

The American Goiter Association has announced that the 1953 meeting will be held in the Drake Hotel, Chicago, May 7-9. The program for the three-day meeting will consist of papers and discussions dealing with goiter and other diseases of the thyroid gland.

WORLD MEDICAL ASSOCIATION

The Board of Regents of the American College of Physicians at its last meeting, November 16, 1952, adopted a resolution endorsing the World Medical Association as a vital and important organization and recommending membership therein by members of the College, if they are so inclined.

The Secretary-Treasurer of the World Medical Association, Dr. Louis H. Bauer, F.A.C.P., has announced the following 1953 meetings which United States members are eligible to attend:

First Western Hemisphere Conference
Richmond, Virginia
April 23-24

First World Conference on Medical Education
London, England
August 22-29

Seventh General Assembly
The Hague, Netherlands
August 31-September 5

Full details are available through Dr. Bauer, 2 East 103rd Street, New York 29, New York.

MEETING, AMERICAN PSYCHOSOMATIC SOCIETY

The Tenth Annual Meeting of the American Psychosomatic Society will take place on April 18 and 19, 1953 at Chalfonte-Haddon Hall in Atlantic City. Four sessions will be held, one of which will be devoted to a panel on the adrenal cortex. Programs of the meeting may be secured from the Society office, 551 Madison Avenue, New York 22, N. Y.

MEETING, AMERICAN COLLEGE OF CARDIOLOGY

The American College of Cardiology will hold its second annual convention at the Statler Hotel in Washington, D. C., June 7, 8 and 9, 1953. The topic will be Diagnosis of Cardiac Diseases. Further information pertaining to the program may be obtained from the Secretary of the College, Philip Reichert, M.D., F.A.C.P., 480 Park Ave., New York 22, N. Y.

AMERICAN LEAGUE AGAINST EPILEPSY ADVANCES TIME LIMIT FOR COMPETITIVE PAPERS

The American League Against Epilepsy has recently announced an extension of the time limit for submission of dissertations for the Jerry Price Memorial Prizes from April 1 to July 1, 1953. The prizes will be awarded for the best dissertation on any aspect of epilepsy submitted by students of approved medical schools in the United States and Canada.

First Prize is \$500. Other prizes up to a total \$1000 will be awarded. Inquiries may be addressed to any member of the Prize Committee: William G. Lennox, M.D., 300 Longwood Avenue, Boston 15, Mass.; Francis L. McNaughton, M.D., 3801 University Street, Montreal 2, Canada; John L. Otto, M.D., 816 Strand, Galveston, Tex.

POSITIONS OPEN IN U. S. CIVIL SERVICE

The United States Civil Service Commission has announced a new examination for medical officers for filling positions in various specialized fields of medicine, with salaries ranging from \$5,940 to \$10,800 a year. The positions are principally in the Bureau of Indian Affairs located on reservations west of the Mississippi River and in Alaska. A few positions may be filled in the Fish and Wildlife Service. Applicants must be fully qualified as doctors of medicine, and for most positions must be currently licensed to practice medicine and surgery in a State or Territory of the United States. Appropriate experience is required.

Further information and application forms may be obtained from the U. S. Civil Service Commission, Washington 25, D. C., or from most first- and second-class post offices. Applications will be accepted until further notice by the Board of U. S. Civil Service Examiners, Bureau of Indian Affairs, Department of the Interior, Washington 25, D. C.

RESIDENCIES IN PSYCHIATRY AVAILABLE

The Veterans Administration Hospital, Lyons, N. J., has available residencies in Psychiatry for a one- to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training can commence at any time, and the program consists of lectures, conferences and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals, and, in addition, there is a series of extensive guest lectures as well as an Annual Institute at the hospital.

ROBERT M. MOORE HEART CLINIC DEDICATED AT INDIANAPOLIS GENERAL HOSPITAL

On February 9, in the Auditorium of the Indianapolis General Hospital, the Robert M. Moore Heart Clinic was formally dedicated as a perpetual memorial to the late Dr. Robert M. Moore, F.A.C.P., former Governor of the American College of Physicians for Indiana. Dr. Harry Plummer Ross, F.A.C.P., Richmond, Ind., President of the Indiana Heart Foundation, presided, and General George E. Armstrong, F.A.C.P., Surgeon General of the U. S. Army, was the speaker of the day. A special tribute was presented to Dr. Cyrus J. Clark, F.A.C.P., who was an intimate friend of Dr. Moore, and who carried on the Clinic activities after Dr. Moore was disabled. Messages were received also from Dr. Irving S. Wright, F.A.C.P., New York City, President of the American Heart Association and Governor of the American College of Physicians for Eastern New York, and from Dr. Kenneth G. Kohlstaedt, F.A.C.P., past President of the Indiana Heart Foundation.

SURVEY OF ARMY HOSPITALS RECENTLY CONCLUDED

A survey was recently conducted in nine of the Army teaching hospitals in the United States by teams that in most instances included an internist, surgeon, and psychiatrist, with experience in teaching. The survey was headed by Dr. Joseph M. Hayman, Jr., F.A.C.P., newly appointed Dean at Tufts College Medical School. Members of the College and the hospitals that they studied included: Dr. Marion A. Blankenhorn, F.A.C.P., Cincinnati, a Regent of the College, Letterman Army Hospital, San Francisco; Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, Valley Forge Army Hospital, Phoenixville, Pa.; Dr. Eugene C. Eppinger, F.A.C.P., Boston, Percy Jones Army Hospital, Battle Creek, Mich.; Dr. Howard P. Lewis, F.A.C.P., College Regent, Madigan Army Hospital, Tacoma, Wash. In addition, Dr. Hayman was a member of the team that inspected the Walter Reed Army Hospital, Washington, D. C.

DR. PAUL D. WHITE RECEIVES FIRST ALBERT LASKER AWARD

Dr. Paul Dudley White, F.A.C.P., Boston, became the recipient of the First Annual Albert Lasker Award for distinguished achievement in the field of cardiovascular disease, presented Feb. 2 by the Albert and Mary Lasker Foundation through the American Heart Association. In making the award, Dr. Irving S. Wright, F.A.C.P., New York, President of the American Heart Association, cited Dr. White for his pioneering efforts in the pathology, diagnosis and treatment of heart disease.

Dr. White was one of the founders of the Association in 1922 and served as its President in 1940-41. His award consists of \$1000 and a gold statuette of the Winged Victory of Samothrace.

Dr. Raymond F. Galt, F.A.C.P., Chicago, has been appointed by the President, with the concurrence of the Board of Regents, as a representative of the American College of Physicians on the Education and Registration Committee of the American Association of Medical Record Librarians.

Dr. Currier McEwen, F.A.C.P., Dean of New York University College of Medicine, has been appointed a member of the Liaison Committee of the American College of Physicians and the American Council on Rheumatic Fever and Congenital Heart Disease, succeeding Dr. Russell Cecil, F.A.C.P., who has resigned.

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, will address the Rotary Club of Atlantic City on an appropriate lay-medical subject on April 14, during the Annual Session of the College. Several local Atlantic City organizations are taking advantage of obtaining eminent medical men as speakers during the College Session.

Dr. Elliott P. Joslin, M.A.C.P., Boston, has recently received two honors. The local American Legion Post presented him with its medal for Americanism in recognition of "his help in establishing the Clara Barton Diabetic Camp for Girls nearby and a similar camp for boys in Charlton, Mass., which bears his name." In addition, the Public Health Service Diabetes Study Center, located in Oxford Town Hall and recently renovated, has been dedicated in his honor.

Dr. Nathan B. Van Etten, F.A.C.P., New York, was one of four former members of the Staff of Morrisania City Hospital to be honored by the Hospital's medical staff. Dr. Van Etten was cited as one "whose scientific and cultural achievements have reflected distinction on (the) institution, not only in this community but in the hospital world." A former President of the American Medical Association, Dr. Van Etten has served the Hospital as President of the Medical Board, Director of Medicine, and Honorary Consulting Physician in his 62 years of medical practice.

Dr. Anton J. Carlson, M.A.C.P., Chicago, was reelected President of the National Society for Medical Research at the annual meeting held Feb. 8 in Chicago. Dr. Andrew C. Ivy, F.A.C.P., Chicago, was reelected Secretary-Treasurer.

Meeting in Seattle, Wash., Jan. 16-17, the Northwest Society for Clinical Research named Dr. Elmer F. Christopherson, F.A.C.P., Vancouver, B. C., President, and elected Dr. Arthur L. Rogers, F.A.C.P., Portland, Ore., Secretary-Treasurer.

At its Second Annual Meeting in Jackson, the Mississippi Heart Association chose Dr. W. K. Purks, F.A.C.P., Vicksburg, President-Elect, and Dr. John G. Archer, F.A.C.P., Greenville, Secretary.

Dr. William A. Sodeman, F.A.C.P., New Orleans, was elected President of the American Society of Tropical Medicine at the annual meeting held in Galveston, Tex., last November.

In addition to the officers previously announced in this journal, Dr. William A. Read, Sr., F.A.C.P., Newport News, was elected Secretary-Treasurer of the Virginia Diabetes Association.

Dr. Joseph Skwirsky (Associate), Newark, was elected Treasurer of the New Jersey Allergy Society at its annual meeting.

Dr. Norman L. Anderson (Associate), Asheville, was named Secretary-Treasurer of the North Carolina Chapter of the American College of Chest Physicians at the Third Annual Meeting held in Asheville.

The Louisiana State Medical Society, meeting recently in Shreveport, chose Dr. Philip H. Jones, F.A.C.P., New Orleans, President-Elect.

Dr. C. Archie Crandell (Associate), Greystone Park, and Dr. Frank P. Pignataro, F.A.C.P., Red Bank, have recently been made President and President-Elect, respectively, of the New Jersey Neuropsychiatric Association.

Under the Presidency of Dr. Walter S. Burrage, F.A.C.P., Boston, the annual meeting of the American College of Allergy was held in the Hotel Statler, Boston, Feb. 26-28. The two days immediately preceding the scientific session were devoted to a postgraduate program, in which Dr. William B. Castle, F.A.C.P., Boston, presented a paper on "Immunological Aspects of Blood Dyscrasias." Dr. Bram Rose, F.A.C.P., Montreal, Can., acted as moderator for a panel on "Allergic Reactions to Penicillin," on which the panelists were Dr. William P. Boger, F.A.C.P., Philadelphia, Dr. William B. Sherman, F.A.C.P., and Dr. Sheppard Siegal, F.A.C.P., both of New York. At a general session, Dr. Chester S. Keefer, Boston, A. C. P. Governor for Massachusetts, talked on "Problems Concerned with the Interpretations of Side Reactions to Antibiotics." After the President's luncheon, which was held Friday at 12:30, Dr. Rose, Dr. Leo H. Crip, F.A.C.P., Pittsburgh; Dr. George Piness, F.A.C.P., Los Angeles; and Dr. J. Warwick Thomas, F.A.C.P., Richmond, Va., were among the collaborators in a clinical conference.

Dr. Jacob Werne, F.A.C.P., New York, made a presentation on "Objectives in the Practice of Forensic Pathology" at the annual session of the American Academy of Forensic Sciences, held in Chicago, Feb. 26-28.

Dr. Louis Krause, F.A.C.P., Baltimore, former College Governor for Maryland, delivered lectures on "Gastrointestinal Problems Seen in General Practice" and on "Old Age—A Promise or a Problem" as part of the postgraduate courses sponsored by the University of North Carolina School of Medicine. The lectures were delivered Feb. 25 at Lumberton, with the Robeson County Medical Society as co-sponsor.

Dr. Samuel A. Levine, F.A.C.P., and Dr. Chester S. Keefer, F.A.C.P., Boston, and Dr. Henry A. Schroeder, Sr., F.A.C.P., St. Louis, were among the guest speakers at the first joint meeting of the Atlantic Graduate Medical Assembly and the South-eastern Section of the American College of Surgeons, held in Atlanta, Feb. 23-25.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., addressed the recently organized Josiah C. Trent Society of the History of Medicine at Duke University

School of Medicine, Durham, N. C., Feb. 17, on "Errors of Priority Credit in Medicine and Surgery—Forgotten Names."

Dr. Oscar O. Miller, F.A.C.P., and Dr. Woodford B. Troutman, F.A.C.P., Louisville, were two of the participants in a telephone seminar that was heard throughout Kentucky on a statewide radio network on Feb. 24. Their discussion concerned "The Significance of Cough."

Dr. Carl V. Moore, F.A.C.P., St. Louis, delivered the Sixth Annual Phi Delta Epsilon lecture, "Iron Metabolism and Iron Deficiency in Anemia," at the University of Minnesota Medical School, Minneapolis, Feb. 17. The following day Dr. Moore addressed the Minneapolis Society of Internal Medicine on "Newer Concepts of Idiopathic Thrombocytopenic Purpura."

At the 161st Annual Meeting of the Connecticut State Medical Society, to be held April 27-29 in Hartford, Dr. Irving S. Wright, F.A.C.P., College Governor for Eastern New York, will discuss "Anti-Coagulant Therapy." Dr. Maurice B. Strauss, F.A.C.P., Framingham, Mass., and Dr. John R. Neeffe (Associate), Philadelphia, will make respective presentations on "Drug Treatment in the Anemias" and "Differential Diagnosis of Jaundice and Application of Liver Function Tests."

Under the Presidency of Dr. Cecil O. Patterson, F.A.C.P., Dallas, the Dallas Southern Clinical Society presented its 22nd Annual Spring Clinical Conference, March 16-19. Guest speakers and their topics included: Dr. Louis H. Clerk, F. A. C.P., Philadelphia, "Paralysis of the Larynx," "Significance of Certain Respiratory Symptoms," "Chronic Cough," "Carcinoma of the Larynx," and "Tumors of the Neck"; Dr. Richard V. Ebert, F.A.C.P., Minneapolis, "The Differential Diagnosis of Cardiac and Pulmonary Dyspnea," "The Diagnosis of Angina Pectoris," and (panel discussion) "Present Status of Heart Surgery"; Dr. O. Spurgeon English, F.A.C.P., Philadelphia, "The Role of Anxiety in Altering Physiological Equilibrium," "Climacteric Neuroses and Their Management," and (panel discussion) "Psychiatric Responsibilities of the Medical Practitioner"; Dr. Richard H. Freyberg, F.A.C.P., New York, "A Critical Appraisal of Cortisone, Hydrocortisone and Corticotropin in Rheumatic Disease," "Gout—Its Nature and Management," and (panel discussion) "Arthritis"; Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn., "Nodular and Ulcerative Lesions of the Lower Extremity" and "Collagen Diseases"; and Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, College Regent, "Functional Disorders of the Gastrointestinal Tract," (panel discussion) "Benign and Malignant Lesions of the Colon," "Drugs Useful in the Treatment of Gastrointestinal Disease," and (panel discussion) "Gastrointestinal Hemorrhage."

"Human Reactions to Stress Situations" was the subject of a three-day symposium held at the Army Medical Service Graduate School in Washington, D. C., March 16-18. Dr. George W. Thorn, F.A.C.P., Boston, participated in a discussion on "The Response of the Pituitary-Adrenocortical System to Situations Provoking Stress"; and Dr. Henry W. Brosin, F.A.C.P., Pittsburgh, talked on "The Reciprocal Relations Between Incentives, Motivation, and Strain in Stressful Situations."

Dr. Roland P. Mackay, F.A.C.P., Chicago, President-Elect of the American Neurological Association, and Dr. I. Arthur Mirsky, F.A.C.P., Pittsburgh, Chairman of the Department of Clinical Science at the University of Pittsburgh School of Medi-

cine, were two of the guest lecturers at Fifth Annual Neuropsychiatric Meeting, which was held at the Veterans Administration Hospital, North Little Rock, Ark., Feb. 26-27.

Dr. Paul Dudley White, F.A.C.P., Boston, was the dinner speaker at the meeting of the South Carolina Heart Association, held in Greenville, Feb. 4. During the scientific session, Dr. White gave a presentation on "Coronary Heart Disease" and jointly conducted a pathological conference with Dr. E. Arthur Dreskin (Associate), Greenville.

Dr. Cornelius P. Rhoads, F.A.C.P., New York, was the principal guest of the North Side Branch of the Chicago Medical Society at a meeting held Feb. 5 in the Drake Hotel. Dr. Rhoads delivered a paper on "Chemotherapeutic Agents in the Treatment of Human Cancer" and acted as moderator of a discussion of "Recent Advances in the Treatment of Cancer."

Dr. Otis L. Anderson, F.A.C.P., Washington, D. C., Chief of the Bureau of State Services, Public Health Service, was one of the chief speakers at a national conference on Home Accident Prevention, held at Ann Arbor, Mich., Jan. 20-22, and sponsored by the University of Michigan and the American Public Health Association.

Under the Presidency of Dr. Sydney G. Margolin (Associate), New York, the American Psychosomatic Society is holding its annual meeting at Atlantic City, April 18-19. Speakers and their topics include: Dr. William N. Chambers, F.A.C.P., Hanover, N. H., "Angina Innocens and Angina Pectoris: A Psychosomatic Study," with Dr. Edward Weiss, F.A.C.P., Philadelphia as the discussant; Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., discussant of "Psychotherapy of Psychosomatic Conditions in the Aged"; Dr. Frank L. Engel (Associate), Durham, N. C., "General Concepts of Adrenal Cortical Functions"; and Dr. I. Arthur Mirsky, F.A.C.P., Pittsburgh, "Psychophysiological Aspects of Adrenal Cortical Function (Experimental)."

Dr. J. Burns Amberson, F.A.C.P., newly appointed President of the Trudeau Sanatorium, was one of the two main speakers at the recent golden anniversary of the Henry Phipps Institute for the Study, Treatment, and Prevention of Tuberculosis, University of Pennsylvania. His subject was "The Treatment of Tuberculosis."

Dr. Franklin D. Johnston, F.A.C.P., Ann Arbor, Mich., discussed "Auscultation of the Heart" at a combined meeting of the Central Ohio Heart Association and the Staff of the University Hospital, held in Columbus, Feb. 9.

Dr. Howard D. Fabing (Associate), Cincinnati, was the guest of the Cabell County Medical Society at their dinner meeting in Huntington, W. Va., Feb. 12. He presented a 20-minute sound movie on "Treatment of Mania" and gave a paper on "Indications for Shock Treatment."

Speakers at the Postgraduate Heart Seminar, sponsored by the Indiana Heart Foundation and the Indiana University School of Medicine and held Feb. 10 in Indianapolis, included Major General George E. Armstrong, (MC), USA, F.A.C.P., the Surgeon General, and Dr. Paul Dudley White, F.A.C.P., Boston.

Under the auspices of the San Diego County Heart Association, an afternoon and evening session on "Heart in Industry" was held in San Diego, Calif., Jan. 21. Among the speakers and their subjects were Dr. Edward M. Kline, F.A.C.P., Cleveland, "The Industrial Physician Can Help" and Dr. Harry E. Ungerleider, F.A.C.P., New York, "Cardiacs in Industry." Dr. Anton S. Yuskis (Associate), President of the Association, acted as moderator at the evening session which included physicians and lay representatives of labor, industry, insurance and vocational rehabilitation.

Dr. Dan L. Urschel, F.A.C.P., of Mentone, Ind., addressed a combined meeting of the Northwestern Ohio Heart Association and the Toledo Academy of Medicine at the Academy Building in Toledo, Ohio, on Feb. 20. The subject of his presentation was "Mean Spatial Vectorcardiography."

The University of Illinois College of Medicine has recently announced the promotion of Dr. Benjamin M. Gasul, F.A.C.P., Chicago, to Clinical Associate Professor of Pediatrics.

Colonel Hugh R. Gilmore, Jr., (MC), USA, F.A.C.P., has recently been appointed Curator of the Medical Museum of the Armed Forces Institute of Pathology in Washington. Colonel Gilmore was formerly Chief of Pathology and of the Allied Sciences Division of the Army Surgeon General's Office.

Dr. Arden Freer, F.A.C.P., Washington, D. C., retired Dec. 20, 1952, as Deputy Chief Medical Director of the Veterans Administration, but will continue to act as a special adviser to the Chief Medical Director. On Dec. 8, 1952, Dr. Freer received the Exceptional Service Medal, the highest award of the Veterans Administration, from General Carl R. Gray, Jr., Administrator. Dr. Kelso A. Carrol, F.A.C.P., Manager of the Veterans Administration Hospital, Hines, Ill., is being transferred to Washington to replace Dr. Roy Wolford, who is assuming Dr. Freer's post as Assistant Chief Medical Director for Professional Service.

Dr. Sidney A. Portis, F.A.C.P., formerly of Chicago, has recently become Head of the Department of Gastro-enterology at the Beverly Hills Clinic, Beverly Hills, Calif. For many years Dr. Portis had been a member of the staff of Michael Reese Hospital and was Clinical Associate Professor of Medicine at the University of Illinois College of Medicine.

Dr. Frank J. Milloy, Sr., F.A.C.P., Phoenix, Ariz., has resigned as Editor-in-Chief of *Arizona Medicine* and as Secretary of the Arizona Medical Association. The main editorial of the December, 1952, Arizona journal paid tribute to his ten years of service and thanked him for his "efficient discharge of the duties entrusted (to him) as a 'good and faithful steward.'" Dr. Milloy had been Secretary of the Association for eight years.

With Dr. Raphael Isaacs, F.A.C.P., Chicago, as Consulting Editor, *Leukemia Abstracts*, a new journal devoted to advancing research in leukemia, has recently been announced by Mr. Herman H. Henkle, Librarian of the John Crerar Library, Chicago. It will be published monthly under the sponsorship of the Lenore Schwartz Memorial Foundation and will consist of abstracts of the world's literature on this disease. Assisting Dr. Isaacs is an advisory committee that includes: Dr. Howard L. Alt, F.A.C.P., Dr. George J. Anday, F.A.C.P., Dr. Andrew C. Ivy, F.A.C.P., Dr.

Leon O. Jacobson, F.A.C.P., and Dr. Louis R. Limarzi, F.A.C.P., of Chicago; Dr. Charles A. Doan, F.A.C.P., Columbus, College Governor for Ohio; Dr. John S. Lawrence, F.A.C.P., Los Angeles; and Dr. Maxwell M. Wintrobe, F.A.C.P., Salt Lake City.

Dr. David I. Macht, F.A.C.P., Baltimore, was honored by the Royal College of Pharmacy of Madrid, Spain, in ceremonies held in the Spanish Embassy in Washington on February 12. The Royal Academy of Pharmacy was founded in 1589, and is one of the oldest and most illustrious scientific institutions. Membership is bestowed only on distinguished scientists "for outstanding contributions to human welfare." Dr. Macht is the first Maryland physician so honored, and the third American. The Academy usually offers its membership to but one man in each nation. Dr. Macht was selected because of his contributions in Pharmacology and Phyto-Pharmacology, the latter field referring to the use of plants rather than animals for finding toxins in the blood.

Dr. Goronwy O. Broun, F.A.C.P., St. Louis, has had his report, "The Clinical Value of Anti-cancer Drugs," chosen by the U. S. State Department for broadcasting "Radio University" over the Voice of America. The report was originally delivered before the recent meeting of the American Association for the Advancement of Science.

Under the will of the late Dr. William Washington Graves, F.A.C.P., St. Louis, the St. Louis University School of Medicine is to receive \$101,380, specifically designated by Dr. Graves, who died in April, 1949, for a special collection of 1000 human skeletons. Director of the Department of Neuropsychiatry for 23 years, Dr. Graves also left most of his collection of books, papers, reprints and correspondence on human anatomy to the School of Medicine.

OBITUARIES

DR. DWIGHT GRISWOLD

Dr. Dwight Griswold (Associate) was born March 22, 1917, in New York City and died of poliomyelitis in Hartford, Conn., on November 8, 1952. He received his A.B. degree from Yale University in 1940 and his M.D. degree from Columbia University College of Physicians and Surgeons in 1943. He interned at St. Luke's Hospital in New York City, 1944-1945, and served his medical residency at the same hospital in 1947-1948.

Dr. Griswold served in the Army Medical Corps in World War II from July, 1945, until March, 1947. As a First Lieutenant, (M.C.), A.U.S., he was Chief of Dispensary and Post Health Inspector at Fort Meade and was a Captain at the Walter Reed Army Hospital.

He came to Hartford to practice medicine in 1948, became a member of the Clinical Assistant Staff at Hartford Hospital, and was advanced to the Assistant Staff in 1951. At the J. J. McCook Memorial Hospital, beginning in 1949, he became in rapid succession Assistant Physician, Assistant Visiting Physician (1951), and Associate Physician (1952). He became the first Director of Medical Education at the McCook Memorial Hospital in 1950, which post he held with outstanding success until his death. He was an active member of the Staff of the Hartford Dispensary and was a trustee of the Hartley Salmon Clinic. In 1952 he was appointed one of the two medical members of the Connecticut Commission on Alcoholism.

Dr. Griswold was a member of the Hartford, the Hartford County and the Connecticut State Medical Societies and the American Medical Association. After successfully completing the written examination of the American Board of Internal Medicine, he became an Associate of the American College of Physicians in April, 1952. Dr. Griswold's publications included one of the first reports on the "Use of Dibenamine in the Diagnosis of Pheochromocytoma," in addition to papers on "Tetanus Following Dental Extraction" and "Cardiac Dysfunction in Hyperthyroidism."

Dr. Griswold's death was an untimely tragedy for medicine, his family, and his numberless friends. His was a spirit of kindness and maturity not often seen in one of his years. He leaves his widow, the former Stratton Nicolson of Washington, D. C.; a son, Dwight, Jr.; and a daughter, Edith. He also leaves a place in the hearts of his patients, friends and colleagues that will be very hard to fill.

JOHN C. LEONARD, M.D., F.A.C.P.,
Governor for Connecticut

DR. WALTER HERMAN NADLER

Walter Herman Nadler, M.D., F.A.C.P., succumbed to an inoperable carcinoma of the right lung on September 13, 1952. Dr. Nadler was born in Peru, Ill., on April 30, 1889. He received his B.S. degree from Northwestern University in 1910 and his M.D. degree from the University's Medical School in 1913. He was a member of the faculty of Northwestern University Medical School throughout his professional life in Chicago and had been Associate Professor of Medicine since 1936.

Dr. Nadler was an interne at Cook County Hospital, 1913-15, having won first place in the highly competitive civil service examinations for a place on the interne staff, where he later served as Attending Physician for eight years. He had also been an Attending Physician at Passavant Memorial Hospital since 1929. Dr. Nadler was Senior Consultant in Internal Medicine at the Veterans Administration Hospital, Hines, Ill., where he had served for more than twenty years.

During World War I he served for two years in France with Base Hospital 12, the Northwestern Unit, as Captain and Major in the Medical Corps of the United States Army.

Dr. Nadler was the author of numerous papers on a variety of subjects in internal medicine and during his early years of practice of internal medicine in Chicago, he was associated with Charles Elliot.

He was a member of Phi Beta Kappa and Alpha Omega Alpha, and in 1939 he was President of the Central Society for Clinical Research. He was a Fellow of the American Medical Association, a Diplomate of the American Board of Internal Medicine, a member of the Chicago Society of Internal Medicine, and a Fellow of the Institute of Medicine of Chicago. Dr. Nadler was a member of the Chicago Pathological Society and the American Diabetes Association. He had been a Fellow of the American College of Physicians since 1944.

In 1927 Dr. Nadler married Augusta Fenger, the daughter of Christian Fenger, a pioneer worker in surgery and pathology in the Midwest. She and two sons, Charles, a second year medical student, and Walter Junior, survive him. He will be missed at Passavant, at Northwestern, in Winnetka, by his colleagues, his patients, and, most of all, by those who were closest to him and knew him best as a constant and devoted husband, loving father, and loyal friend.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. MORRIS HENRY NATHANSON

Morris Henry Nathanson, M.D., F.A.C.P., died April 24, 1952, of coronary thrombosis. Dr. Nathanson was born in Minneapolis, Minn., September 15, 1892. He was graduated from the University of Minnesota in 1916 with the degree of Bachelor of Science, and in 1919 he received his M.D. degree from the University of Minnesota Medical School.

From 1919 until 1937 Dr. Nathanson was a member of the faculty of the University of Minnesota Medical School, beginning as an Assistant in the Department of Medicine and later becoming Associate Clinical Professor of Medicine. A member of the Associate Staff of the Minneapolis General Hospital, he was also on the staffs of the Asbury and St. Mary's Hospitals in Minneapolis.

Appointed Associate Clinical Professor of Medicine at the University of Southern California School of Medicine in 1937, Dr. Nathanson moved to Los Angeles, where, besides his teaching duties, he was Senior Attending Physician at the Los Angeles County Hospital and the Cedars of Lebanon Hospital.

In addition to holding memberships in state and local societies in Minnesota and California, Dr. Nathanson was a member of the American Medical Association, the Central Society for Clinical Research, the Society for Experimental Biology and Medicine, and the American Society for Pharmacology and Experimental Therapeutics. He was a member of Sigma Xi and Alpha Omega Alpha fraternities as well as a Diplomate of the American Board of Internal Medicine. The author of many publications and papers, Dr. Nathanson had been a Fellow of the American College of Physicians since 1936.

DR. HAROLD ORR

Dr. Harold Orr, F.A.C.P., died on December 26, 1952, in Toronto. He was born in Toronto in 1889 and received his medical training at the University of Toronto, graduating in 1911. Following an internship in St. Michaels Hospital, Toronto, he began general practice in Medicine Hat, Alberta.

Dr. Orr served with distinction as a medical officer in the R.C.A.M.C. during World War I, being decorated by both the British and French governments for distinguished service. Following this period, Dr. Orr became interested in preventive medicine, dermatology and syphilology. He carried out graduate training in these fields at the University of Toronto and in London, England. In 1924 Dr. Orr was appointed Clinical Professor of Dermatology in the University of Alberta School of Medicine, serving in that capacity until his death. He was a stimulating teacher and was an active member of the staff of the University of Alberta Hospital.

Dr. Orr served as Director of the Division of Social Hygiene for the province of Alberta and was active in the organization of the Board of Health of the city of Edmonton. He was a leader in organized medicine, having been President of the Edmonton Academy of Medicine, President of the Alberta Division of the Canadian Medical Association, and at the time of his death was President of the Canadian Medical Association. A Fellow of the Royal College of Physicians and Surgeons of Canada, Dr. Orr had been a Fellow of the American College of Physicians since 1942.

During his active tenure of office as President of the Canadian Medical Association, Dr. Orr showed enthusiasm, ability and untiring zeal. He developed his final illness on his return journey from the World Medical Association meeting in Athens. In addition to his professional interests, Dr. Orr was a public-spirited citizen. He was President of the Edmonton Museum of Art for many years and acted as Chairman of the Community Chest Committee in Edmonton for two years.

Dr. Orr had an attractive, kindly, dynamic personality with remarkable executive ability. His untimely death will create a loss to the profession of medicine throughout Canada and to his many colleagues and friends.

JOHN W. SCOTT, M.D., F.A.C.P.,
Governor for Alberta and British Columbia

DR. EVANS WILLIAM PERNOKIS

Evans William Pernokis, M.D., F.A.C.P., died of coronary artery sclerosis on November 9, 1952. Dr. Pernokis was born on May 5, 1898, in Sparta, Greece. He did his college work and premedical studies at the University of Chicago and received his M.D. degree in 1923 from Harvard University Medical School. He was an interne and resident physician at Presbyterian Hospital of Chicago from 1923 until 1927. Following the hospital training, he did postgraduate work at the universities of Berlin, Vienna, and Zurich.

He was a Diplomat of the National Board of Medical Examiners and the American Board of Internal Medicine. He became a Fellow of the American College of Physicians in 1943. At Rush Medical College he served in various capacities between 1924 and 1942, from Clinical Assistant in Medicine to Associate Clinical Professor of Medicine. At the University of Illinois College of Medicine he was Associate Clinical Professor of Medicine from 1942 until his death. Dr. Pernokis was Associate Attending Physician at Presbyterian Hospital for many years.

His main interest in Internal Medicine was hematology, and most of his published papers are in this field. During World War II he served as a Commander in the Medical Corps of the United States Naval Reserve. He was a Fellow of the Institute of Medicine of Chicago, and a member of the American Medical Association, Chicago Medical Society, Illinois State Medical Society, and the Chicago Society of Internal Medicine.

Dr. Pernokis was a modest, kind, and just man, always giving the best he had in him to his patients. He was loyal and devoted to his family, his friends, his col-

leagues, and his patients. All who came in contact with him soon realized that Dr. Pernokis was a man of high ideals who was devoted to the medical profession.

He is survived by his wife, Olga, and one daughter, Patricia.

HOWARD WAKEFIELD, M.D., F.A.C.P.,

Governor for Northern Illinois

DR. WILLIAM THOMAS SALTER

William Thomas Salter, M.D., F.A.C.P., was born in Boston, Mass., December 19, 1901, and died in New Haven, Conn., on July 30, 1952. He received his A.B. degree from Harvard University in 1922 and his M.D. degree from Harvard Medical School in 1925. He interned at the Massachusetts General Hospital from 1925 to 1927 and was Resident and Research Fellow from 1927 to 1928. He was Harvard's Moseley Traveling Fellow from 1928 to 1929 and Research Fellow in Medicine at Harvard from 1929 to 1932, as well as Tutor in Biochemical Sciences at Harvard from 1929 to 1939. For this latter period he was also Research Fellow in Biochemistry, Harvard Cancer Commission. He was Faculty Instructor in Medicine at Harvard from 1932 to 1934, Assistant Professor at Harvard Medical School from 1934 to 1941 and was Professor of Pharmacology and Chairman of the Department at Yale University School of Medicine from 1941 until his death.

Dr. Salter was a member of the American Academy of Arts and Sciences, American Association for the Advancement of Science, American Association for Cancer Research, American Association of the History of Medicine, American Chemical Society, American Institute of Nutrition, American Physiological Society, American Society for Clinical Investigation, Association of American Physicians, Association for the Study of Internal Secretions, Biochemistry Society (England), Boston Medical History Club, Classical Association of New England, History of Science Society, New York Academy of Sciences, the Society for Experimental Biology and Medicine, Psychosomatic Medicine, American Association for the Study of Goiter, Massachusetts Medical Society, Connecticut State Medical Society, and the American Medical Association, and an honorary member of the Society of Pharmacology and Therapeutics of the Argentine Medical Association.

He was a member of Sigma Xi, Phi Beta Kappa, and Alpha Omega Alpha. Dr. Salter had been Chairman (1950), Central Committee on Scope, U. S. Pharmacopoeia, and had been a Fellow of the American College of Physicians since 1941. His "Text-book of Pharmacology" was published in March, 1952.

Dr. Salter is survived by his wife, nee Eleanor Vallandingham, and three daughters, Frances, Eleanor and Katherine. He was a kind, helpful, enthusiastic and brilliant physician, teacher and investigator. His life was full to overflowing with worth-while activity, but he was never too busy to be helpful to his medical colleagues and to his friends. His passing has left a place that will be most difficult to fill, but his cheerful spirit and inspiration will live long in the hearts of all who were fortunate enough to have had contact with him.

JOHN C. LEONARD, M.D., F.A.C.P.,

Governor for Connecticut

DR. HYMAN A. SLESINGER

Dr. Hyman Abraham Slesinger, F.A.C.P., died on September 4, 1952, of coronary occlusion. Born in Windber, Pa., July 8, 1904, he was graduated from the University of Pittsburgh School of Medicine in 1926. Following an internship in the Windber Hospital, he devoted his time to pediatrics and became a Diplomate of the American Board of Pediatrics in 1939. In addition to his work in pediatrics, he was Consultant Pathologist for the State Tuberculosis Hospital at Cresson, Pa., and Consultant Cardiologist for the Veterans Administration, Johnstown.

Dr. Slesinger was a Lieutenant Colonel in the United States Army Medical Corps and served overseas from 1943 to 1946. He was a Fellow of the American Academy of Pediatrics and the American Academy of Allergy. He became a Fellow of the American College of Physicians in 1939.

C. HOWARD MARCY, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. JOHN MAIRS THORNE

Dr. John Mairs Thorne, F.A.C.P., was born in Hastings, Minn., on January 11, 1865; he died in Fox Chapel, Pa., May 5, 1952, having spent his professional career in the Pittsburgh area.

After receiving his M.D. degree from Jefferson Medical College of Philadelphia in 1886, Dr. Thorne served his internship at the Western Pennsylvania Hospital in Pittsburgh. Dr. Thorne then became Surgeon and Visiting Surgeon, respectively, at the McKeesport Hospital and the South Side Hospital. At this stage of his career Dr. Thorne developed an interest in internal medicine and became Visiting Physician and later Internist at the Presbyterian Hospital, where he served for a number of years. Dr. Thorne was also Consulting Internist at the Dixmont State Hospital and Consulting Physician at the Woman's Hospital. For a number of years he also taught at the University of Pittsburgh School of Medicine and was Emeritus Associate Professor of Medicine.

In 1917 Dr. Thorne served as President of the Allegheny County Medical Society and was a former Vice President of the Academy of Medicine of Pittsburgh. He was also a member of the American Therapeutic Society and was a Diplomate of the American Board of Internal Medicine. He became a Fellow of the American College of Physicians in 1917.

DR. BURBRIDGE SCOTT YANCEY

Burbridge Scott Yancey, M.D., F.A.C.P., was born in Harrisonburg, Va., on February 3, 1902. He had both his academic and medical training at the University of Virginia and graduated in medicine there in 1926. After one year's internship in the U. S. Marine Hospital in Baltimore, he returned to his home community for private practice of medicine. He was active in all phases of medical activity and became a well known internist in that community, where he continued to serve until his death on November 9, 1952.

Dr. Yancey had been on the medical staff of the Rockingham Memorial Hospital since 1932 and was a member of the Southern Medical Association, the Virginia State Medical Society, Rockingham County Medical Society, Shenandoah Valley Medical Association, and the American Medical Association; he had been a Fellow of the American College of Physicians since 1939.

He had always manifested a keen interest in the American College of Physicians, its activities and its meetings, and was a regular attendant at the annual regional meetings.

Dr. Yancey suffered a coronary occlusion several years ago and as a result was forced to limit his work. He had, however, continued in active practice until last fall when, after an attack of cholecystitis and subsequent surgery, he had another occlusion which was the cause of his death.

For a number of years Dr. Yancey had been the only member of the College in his community, and his absence will be keenly felt.

CHARLES M. CARAVATI, M.D., F.A.C.P.,
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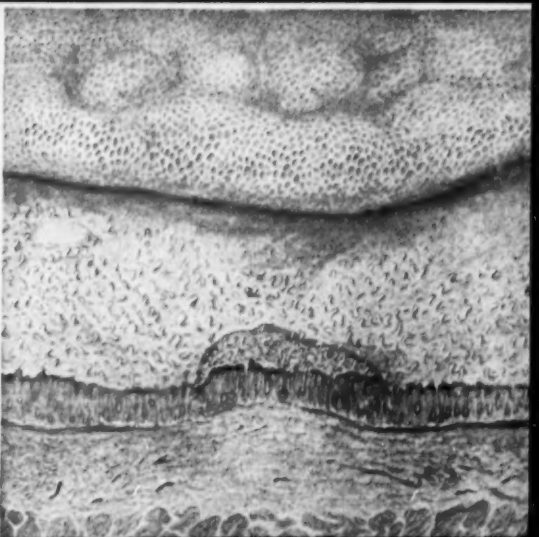
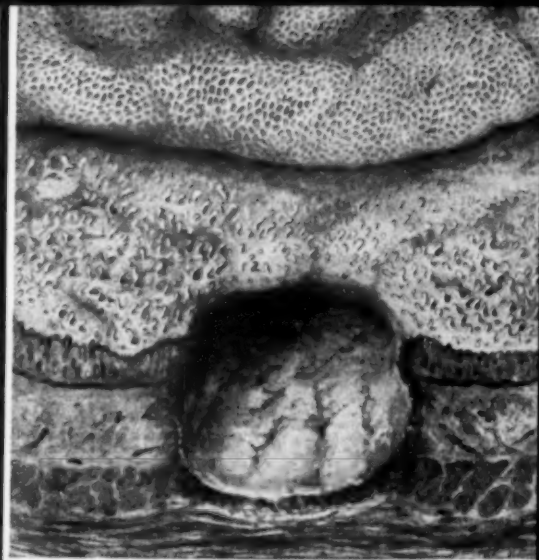
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Bottom—Healed ulcer with restoration of mucosa.





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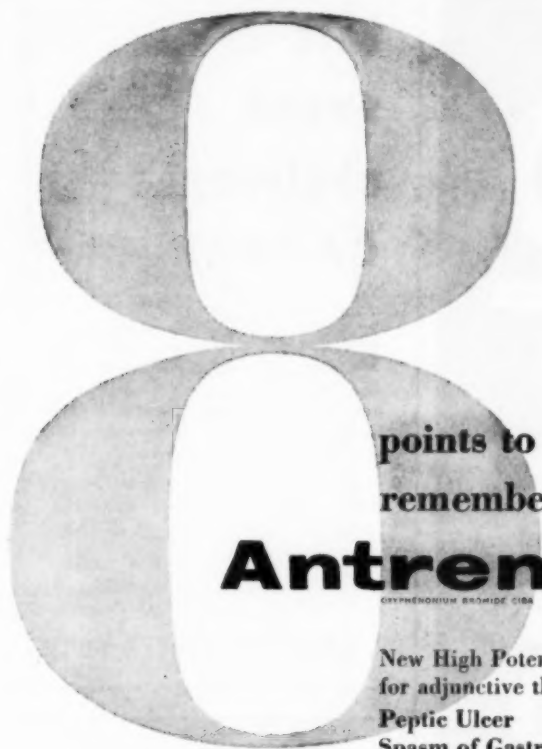
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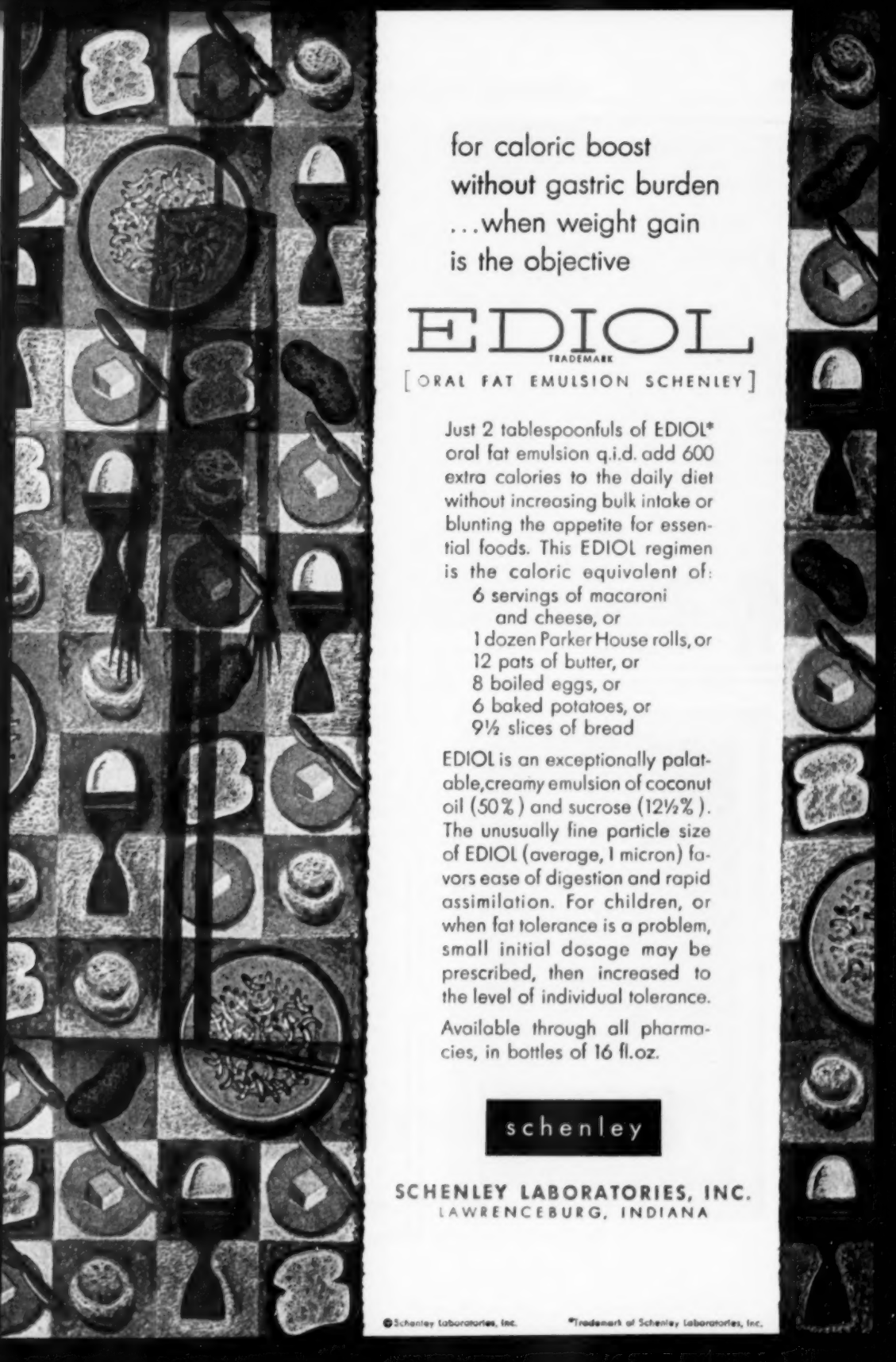
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1. Humphreys, P., et al.: *Angiology* 3:1 (Feb.) 1952.
2. Plotz, M.: *New York State J. Med.* 52:2012 (Aug. 15) 1952.
3. Perlman, A.: *Angiology* 3:16 (Feb.) 1952.

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